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Paracetamol Poisoning and its Treatment in Man

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Doctorate of Philosophy

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Declaration

I hereby declare that the work presented in this thesis is my own, except where stated in the text. The work has not been submitted in any previous application for a degree.

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Abstract

Title: Paracetamol poisoning and its treatment in man

Paracetamol is the most common drug taken in overdose in the UK. Although it has been used in overdose for about 50 years, there are many aspects of its toxicity and treatment that are not fully understood. In this thesis a series of related studies on paracetamol overdose are reported. The nephrotoxic effects of paracetamol in overdose have long been recognised. To better understand the mechanisms of this effect the effect of acute paracetamol overdose on plasma electrolytes were investigated, both retrospectively and, more intensively, prospectively. The results of these studies showed paracetamol overdose is associated with dose-related hypokalemia, and kaliuresis of short duration (<24h), suggesting a specific renal effect of paracetamol in overdose, perhaps via cyclo-oxygenase inhibition. This effect seems distinct from any nephrotoxic effect of paracetamol. In the third study the possible impact of features at admission, including renal impairment, on outcomes in a large cohort of patients who developed severe liver injury following paracetamol overdose was evaluated retrospectively. The key finding was that plasma creatinine, and gamma glutamyl transpeptidase, at first admission appeared to be useful predictors of poor outcome. The last three studies focus on antidote treatment of paracetamol overdose. Intravenous acetylcysteine (NAC) has been used as treatment of choice for over 30 years in patients who are at risk of hepatotoxicity. There are reports of liver failure and death in patients who have “non-toxic” plasma paracetamol concentrations on the UKL nomogram, and who are therefore not treated. To better understand this, the frequency of liver failure in patients who had low paracetamol was assessed by examining retrospective data from the Scottish Liver Unit over a 12-year period. Similar data was collected in the University of Newcastle upon Tyne by colleagues there. Only a small percentage of patients developed hepatotoxicity when initial paracetamol was low. It was concluded that on a cost-benefit basis the current thresholds for antidote treatment should not be lowered. The final 2 studies examine adverse reactions (ADRs) to NAC, a common clinical problem. The pattern and mechanisms of ADRs in man are not well described or understood. Factors influencing the frequency of adverse effects were studied in a prospective manner. Paracetamol concentration and male gender were protective and family history of allergy was a risk factor for adverse effects in this cohort. In a smaller focussed study the roles of histamine and other biomarkers as underlying pathophysiological mechanisms in ADR occurrence were studied. The severity of ADRs correlated with the extent of histamine release, which was independent of tryptase increase, suggesting a non-mast cell source. The mechanisms by which paracetamol might lessen histamine release require further investigation.

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"You who have attained to faith! Be patient in adversity, and vie in patience with one another, and be ever ready and remain conscious of God, so that you might attain to happy state" Imran verse 200.

I am praising him for granting me his mercy and the strength through the adversities of life.

This work was performed over more than 4 years, during which I was a postgraduate student at the University of Edinburgh and a Clinical Research Fellow in the toxicology unit and NPIS Edinburgh (Scottish Poisons Information Bureau) in the Royal Infirmary of Edinburgh.

The topic of paracetamol toxicity and its treatment in man was originally proposed by Professor DN Bateman. The nephrotoxic aspect of the study was proposed by Dr J Goddard. They guided me initially through the controversies in the field and were both responsible for the supervision of my project. I am most grateful for their advice and the opportunities they gave me to perform this research. Thanks especially to my primary supervisor, Professor DN Bateman for his time spent reviewing this project.

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With all my love

To my father, whose best wishes have always inspired me.
In memory of my mother, especially for the impact of her strong character on me.

To my other family members, for their kind support and encouragement.

I dedicate this thesis to my father

List of Publications

1. Full paper: Beer C, Pakravan N, Hudson M *et al*. Liver unit admission following paracetamol overdose with concentrations below current UK treatment thresholds. Published in *QJM.* 2007; 100:93-96 (see appendices).

2. Full paper: Pakravan N, Bateman DN, Goddard J. Effect of acute paracetamol Overdose on changes in serum and urine electrolytes. Published in *Br.J.Clin.Pharmacol.*2007; 64:824-832 (see appendix).

3. Letter: Pakravan N, Goddard J, Bateman DN. Hypokalaemia following Paracetamol overdose. Published in *Ann.Clin.Biochem.* 2008; 45:111-112 (see appendices).

4. Full paper: Pakravan N, Waring WS, Sharma S, Ludlam C, Megson IL, Bateman DN. Risk factors and mechanisms of anaphylactoid reactions to acetylcysteine in acetaminophen overdose. Published in American *Journal Of Clinical Toxicology*. September 2008: 46 (8): 697-702 (see appendices).

5. Full paper: Pakravan N, Simpson KJ, Waring WS, Bates CM, Bateman DN. Renal injury at first presentation as a predictor for poor outcome in severe paracetamol poisoning preferred to a liver transplant unit. Published in *European Journal of Clinical Pharmacology*, October 2008 (see appendices).

List of Presentation

1. Talk presentation in Scottish Renal Association, Dundee, UK, November 2004

2. Poster presentation in British Association of Clinical Pharmacology (BPS), Newcastle, UK, December 2004.

3. Poster presentation in British Association of Clinical Pharmacology (BPS), Oxford, UK, December 2006 (nominated for Young Scientist Award)

4. Poster presentation in European Association of Poisons Centres and Clinical Toxicologist (EAPCCT), Athens, Greece, May 2007

5. Poster Presentation in the North American Association of Clinical Toxicologist (AACT), New Orleans, USA, October 2007.

6. Talk presentation in European Association of Poisons Centres and Clinical Toxicologist (EAPCCT), Seville, Spain, May 2008 (Winner of Young Scientist Award)

7.Poster Presentation on " Mechanisms of adverse reaction to IV acetylcysteine in acetaminophen overdose" presented by Prof DN Bateman in the North American Association of Clinical Toxicologist (AACT), held on Sept 2008 in Toronto.

9. 3 talk presentations in Clinical Pharmacology Unit meetings, in Western General Hospital and Queen Margaret Institute (QMRI), Edinburgh, UK

10. 4 Talk presentations in TRIM meetings, Royal Infirmary of Edinburgh, Edinburgh, UK.

List of Abbreviations

A II: angiotensin II
ADH: anti-diuretic hormone
ADRs: adverse reactions
ALT: alanine transaminase
AM404: N-arachidonyol-phenolamine
ANOVA: analysis of variance
ARF: acute renal failure
AUC: area under the curve
CNS: central nervous system
COX: cylco-oxygenase
Cr: creatinine
[Cr]: plasma creatinine concentration
CRP: C-reactive protein
CYP1A2: cytochrome 1A2
CYP2E1: cytochrome 2E1
DBP: Diastolic blood pressure
DIC: disseminated intra vascular coagulation
ECF: extracellular fluid
ECG: electrocardiogram
EDTA: Ethylene Diamine Tetra Acetic acid
HETEs: hydroxyeicosatetraenoic acids
EETs: epoxyeicosatrienoic acids
ELIZA: Enzyme-Linked Immuno Sorbent Assay
F: Female
Fe: fraction of excretion
FeK: fraction of excretion of potassium
FeMg: fraction of excretion of magnesium
Fe_{Na}: fraction of excretion of sodium
FePO4: fraction of excretion of phosphate
GI: gastrointestinal
GGT: gamma glutamyl transpeptidase
GFR: glomerular filtration rate
GSH: glutathione
h:hour
HCL: hydro chloric acid
HCO3: bicarbonate
[HCO_3]: plasma bicarbonate concentartion
HIV: human immunodeficiency virus
ICF: intracellular fluid
Ig E: Immunoglobulin E
IL-6: interleukin 6
ITU: intensive care unit
IQR: inter quartile range

IV: Intravenouse
K: potassium
[K]: plasma potassium concentartion
KCH: King's College Criteria
K_U :urinary potassium
K_S: serum potassium
M: male
Mg: magnesium
Min: minute
Mm: milli metre
Mm: milli mol
mmHg: millimetre mercury
Na: sodium
[Na]: plasma sodium concentartion
NADPH: nicotinamide adenine dinucleotide phosphate
NAKA: sodium-potassium ATPase
NAPQI: N-acetyl-p-benzoquinoneimine
NAC: N-acetylcysteine, N-acetylcysteine or parvolex
NHCL4: ammonium chloride
NMDA: N-methyl-D-aspartate
NSAID: non-steroidal anti-inflammatory drug
O2 sat: oxygen saturation
PG: prostaglandin
PGE_2: prostaglandin E_2
PEFR: peak expiratory flow metre rate
PAH: p-aminohippuric acid
PGI_2: prostaglandin I_2
PO4: phosphate
PR: pulse rate
PT: prothrombin time
PRA: plasma renin activity
PT: prothrombin time
RBF: renal blood flow
RBP: retinol binding protein
ROC: Receiver operator characteristics
SBP: systolic blood pressure
Sem: standard error of the mean
SIADH: syndrome of inappropriate anti diuretic hormone
SLTU: The Scottish Liver Transplant Unit
S_{Osm}: serum osmolality
SSRI: selective serotonine reuptake inhibitor
T: temperature
TmP/GFR: Renal threshold of phosphate
tPA: tissue plasminogen activator
TRP: total reabsorbed phosphate

TTKG:Trans tubular potassium gradient
TX: thromboxane
TXA_2: thromboxane A_2
TXB_2: thromboxane B_2
U_{Cr}: urinary creatinine
UK: United Kingdom
U_{Na}:Urinary sodium
U_{Osm}: urine osmolality
US: United State
vWf: von Willebrand factor

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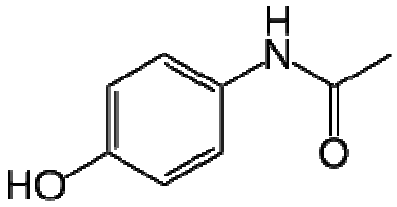
Chapter I: Introduction and Literature Review of Paracetamol Toxicity



Paracetamol: N-(4-hydroxyphenyl) acetamide

1-1: Introduction

The name “paracetamol” known as acetaminophen in the US, derives from its chemical name para-acetylaminophenol. Paracetamol was first synthesised by Morse in Germany in 1878 and it was used clinically as an antipyretic by Von Mering in 1887 [1] only for a short period, but was discarded in favour of phenacetin because it was assumed that it was less toxic than paracetamol. In 1893, paracetamol was discovered in the urine of individuals who had taken phenacetin. In 1899, paracetamol was found to be a metabolite of acetanilide; however nobody realised the importance of this discovery at the time.

In 1948, Brodie and Axelrod’s work led to rediscovery of paracetamol. They elegantly demonstrated that the therapeutic effect of phenacetin was due to its active hepatic metabolite, paracetamol, and since it did not have the toxic effects of phenacetin, they advised use of paracetamol as an analgesic in medical treatment [2]. In 1955, for the first time McNeil laboratories in the US sold the product under the brand name of Tylenol Children’s Elixir as an analgesic and antipyretic in children [3].

Paracetamol was introduced to the UK market in 1956. Frederick Stearns & Co sold 500 mg tablets of paracetamol under the brand name of Panadol as a prescribed pain killer and antipyretic. In 1958, Panadol Elixir, a children’s

formulation, was introduced. In 1963, paracetamol was added to the British National Formulary. Concern about safety postponed its widespread acceptance, but, when phenacetin was finally withdrawn from the market because of nephrotoxicity in the 1970's, paracetamol became widely used as an analgesic replacement [4]. Due to its few side effects and less interaction with other drugs it gained significant worldwide popularity among analgesics and it became the most commonly prescribed drug in children [5].

The main topics of study in this thesis are the renal effects of paracetamol, and the adverse reactions caused by intravenous infusion of acetylcysteine (NAC), a treatment of choice in paracetamol overdose. This introductory chapter includes three separate parts. In the first part pharmacology and toxicology of paracetamol will be discussed. In the second part renal physiology and the pathophysiology of renal dysfunction, in particular toxic effects of paracetamol on the kidney are reviewed. Finally in the last part NAC treatment and the mechanisms of its adverse reactions in paracetamol overdose are discussed.

1-2: Pharmacology & Toxicology of Paracetamol

1-2-1: Pharmacodynamics

The main therapeutic effects of paracetamol are analgesia and antipyresis; it also has a weak anti-inflammatory effect [6]. Although paracetamol has been in clinical use for over half a century, the precise mechanisms of the analgesic and

antipyretic effects of paracetamol are still unclear. Like classical non-steroidal anti inflammatory drugs (NSAIDs), paracetamol reduces production of prostaglandins (PG), a family of pro-inflammatory chemicals, through inhibition of cyclo-oxygenase (COX) enzymes. Unlike classical NSAIDs however, paracetamol does not have important anti-inflammatory effects [1;7-9]. However, some studies have suggested that paracetamol may have mild anti-inflammatory effects. Paracetamol, like selective COX-II inhibitors, decreases PG concentrations in vivo, but unlike COX- II inhibitors does not suppress severe inflammation [8]. A recent study on healthy volunteers given 1000 mg paracetamol orally showed that paracetamol inhibited COX-II by more than 80%, i.e. a degree comparable to NSAIDs and selective COX-II inhibitors [10]. This study also showed that inhibition of COX-I as measured by thromboxane B_2 (TXB_2) synthesis was minor (56%) and not sufficient for suppression of platelet function. These data support an anti-inflammatory action of paracetamol, and indicate why it has a superior overall gastrointestinal safety profile compared with non-steroidal anti-inflammatory drugs (NSAIDs).

In animal studies the antipyretic and analgesic effects of paracetamol have been shown to be mediated through COX-III inhibition, a new variant of COX-I, [11;12]. However, low level of expression of COX-III in man suggests little clinical relevance at therapeutic doses [13]. Some studies suggest that the central nervous system (CNS) is the site of the anti-nociceptive effect of paracetamol [14;15]. Other suggested mechanisms for the analgesic effects of

paracetamol are inhibition of nitric oxide generation, and effects on either N-methyl-D-aspartate (NMDA) or substance P [16]. Recently, an active conjugate of paracetamol has been suggested as a mediator of the analgesic effects of paracetamol [17]. In this novel metabolic pathway, following deacetylation of paracetamol to its primary amine, which occurs mainly in liver, this amine is conjugated with arachidonic acid in the CNS to form N-arachidonyol-phenolamine (AM404). AM404 is postulated to be involved in the analgesic effect of paracetamol through its effect on endogenous cannabinoid systems [17].

1-2-2: Pharmacokinetics

The therapeutic dose of paracetamol is 10-15 mg/kg with a therapeutic index of approximately 10 [18]. The adult oral dose of paracetamol for

analgesic and antipyretic effects is 650-1000 mg every 4h, with a maximum daily dose of 4g. Following oral ingestion of regular release tablets, paracetamol is rapidly absorbed and reaches peak concentration within approximately 45 minutes. Time to peak for liquid paracetamol is 30 minutes, but food prolongs time to peak concentration [19;20]. Peak concentration after recommended dose ranges from 8-32 mg/l. Bioavailability of paracetamol is 60-98% with protein binding of 10-30% at therapeutic doses [19]. Paracetamol passes through the blood brain barrier [21] and placenta [22].

The liver is the main organ for metabolism of paracetamol, eliminating 25% of the therapeutic dose by first pass metabolism. In adults the majority of paracetamol (approximately 90%) is conjugated with glucuronide (40-67%), sulphate (20-46%) and cysteine (3%), forming inactive and harmless metabolites (Figure 1.1) [1]. In premature infants, newborns, and young infants the majority of paracetamol is metabolised by sulphation [23]. Less than 5% is excreted unchanged in the urine.

A small, yet significant fraction, ranging from 5-15% is metabolised via the hepatic cytochrome P450 enzyme system (cytochrome 2E1: CYP2E1 and cytochrome 1A2: CYP1A2 isoenzymes) resulting in the formation of a highly toxic metabolite N-acetyl-p-benzoquinoneimine (NAPQI). Glutathione is immediately conjugated with this intermediate metabolite resulting in formation of non-toxic cysteine and mercaptate conjugates, which are excreted in urine [24-29] (Figure 1.1).

Some drugs such as carbamazepine, phenobarbital, phenytoin, primidone, and rifampicin induce cytochrome P450 enzymes and thus increase subsequent production of this toxic metabolite (NAPQI) [30;31]. The interaction between paracetamol metabolism and ethanol ingestion is complex and its implication in acute overdose remains controversial. In chronic alcoholism the combination of hepatic enzyme induction and

glutathione depletion seems to increase paracetamol toxicity. In contrast, acute alcohol ingestion reduces toxic metabolic activation due to competitive inhibition, and depletion of cytosolic NADPH (nicotinamide adenine dinucleotide phosphate) and therefore, plays a protective role in hepatotoxicity [32-37].

1-2-3: Toxicokinetics

In general paracetamol, when taken in therapeutic dose, is a safe drug. The lowest dose which is generally thought to be capable of causing toxicity is considered 7.5 g in adults and 150 mg/kg in children [19]. It is believed that toxicity generally occurs above 150 mg/kg [18]. Even after taking a toxic dose, the majority of paracetamol absorption occurs within 2h and is thought to reach peak plasma levels by 4h [19]. There are case reports of later peaks in overdose, particularly in co-ingestion with other drugs that delay gastric emptying [38] or following ingestion of an extended release of paracetamol preparation [39].

Figure 1.1: Metabolism of paracetamol (From [1])

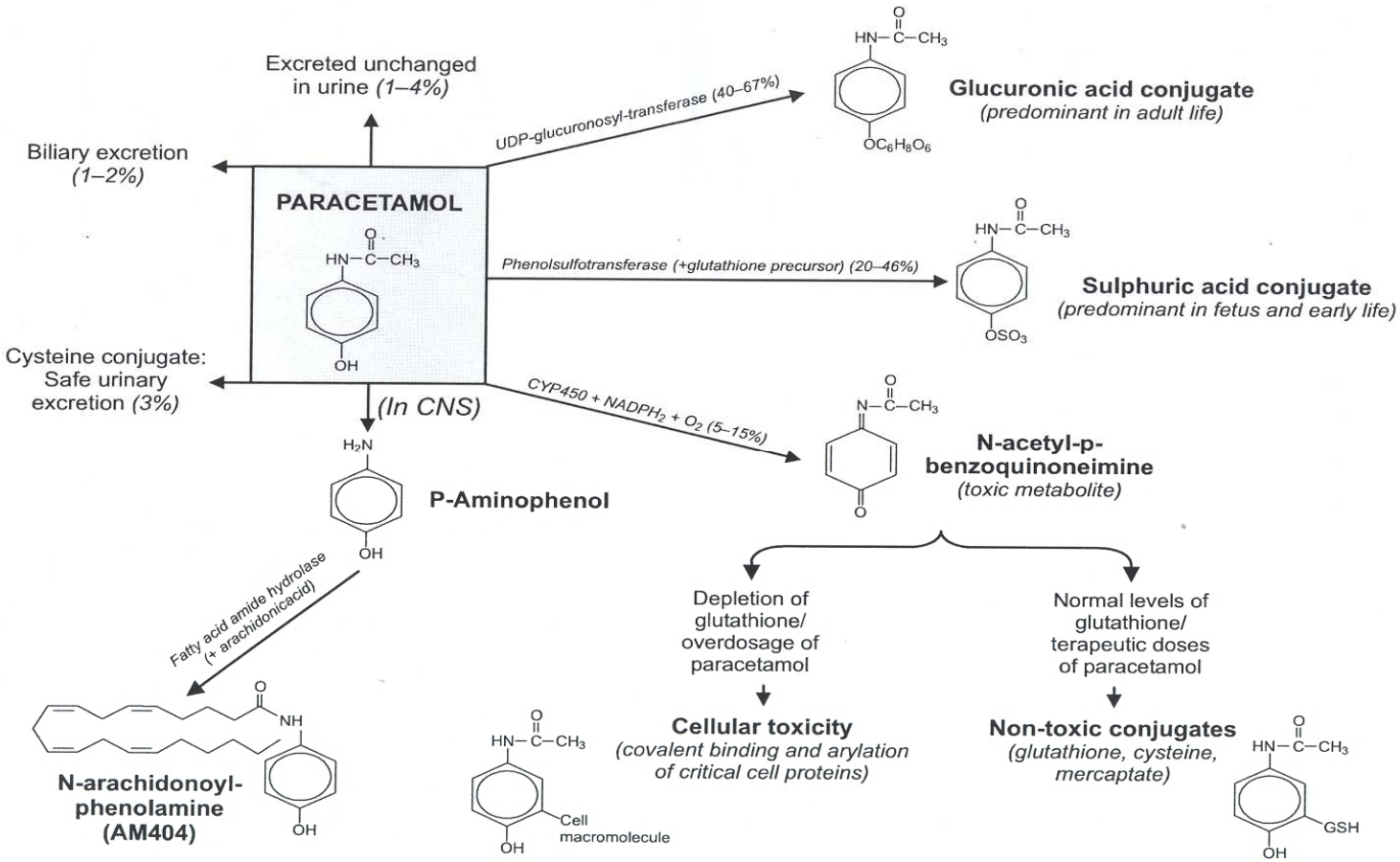


Fig. 3. Metabolism of paracetamol in humans.

1-2-3-1: Epidemiology of toxicity

Paracetamol has been available as an over-the-counter drug (without prescription) since 1956, and has a remarkable safety record. 30 million packs containing paracetamol are sold in the UK every year [40]. The first report of paracetamol toxicity in man was in 1966 [41;42]. It is now the most commonly drug used in deliberate self harm in the UK [43-46] and is involved in 48% of poisoning admissions to hospital [47]. This trend is not confined to the UK and has also been reported in other European countries [48;49], and the US [50]. Every year, around 70,000-100,000 cases of paracetamol poisoning occur in Britain [43;45]. The liver and kidney are the main targets involved in paracetamol toxicity.

1-2-3-2: Hepatotoxicity

1-2-3-2-1: Epidemiology of hepatic toxicity

Paracetamol is the commonest cause of fulminant hepatic failure and liver transplantation in the UK and in the US [51-56]. The estimated number of deaths in the UK following paracetamol poisoning is currently at least 150 per year [57-59]. The death rate in England and Wales between 1993 and 1997 was higher at 500 per year [60]. Mortality in Scotland has been shown to be twice as high as England and Wales [61]. Following restricting paracetamol pack sizes in September 1998 [62] there have been conflicting reports in regards to effect on

hospital admission, admission to liver units and liver transplantation and mortality rate following paracetamol overdose. While the new legislation was initially shown to reduce mortality and morbidity following paracetamol overdose in England and Wales [63], in Scotland restricting paracetamol pack sizes has not had a significant effect on mortality [64]. Later data for England supports the Scottish evidence [65] .

1-2-3-2-2: Pathophysiology of hepatotoxicity

The liver is the main target of acute paracetamol toxicity. The safety of therapeutic dose of paracetamol results from the availability of electron donors such as glutathione (GSH) and other thiol-containing compounds. When paracetamol is taken in appropriate dose glutathione supply far exceeds that which is required to detoxify the toxic metabolite, NAPQI, and therefore no toxicity occurs. In overdose the rate and quantity of formation of toxic metabolite, NAPQI, exceeds glutathione supply. The highly reactive NAPQI rapidly binds to cellular macromolecules containing cysteine. This covalent binding causes hepatocellular necrosis, predominantly in the centrilobular zone (Zone III), due to local formation of NAPQI [19;26;66-68]. In severe toxicity, necrosis may destroy the entire liver parenchyma. Severe cases develop fulminant hepatic failure [54]. Children with acute febrile illness [66;69] and patients taking P450 enzyme inducing drugs and ethanol [70] are at greater risk of hepatotoxicity. Malnutrition, when the glutathione supply is inadequate (less than 30% of normal) is also a

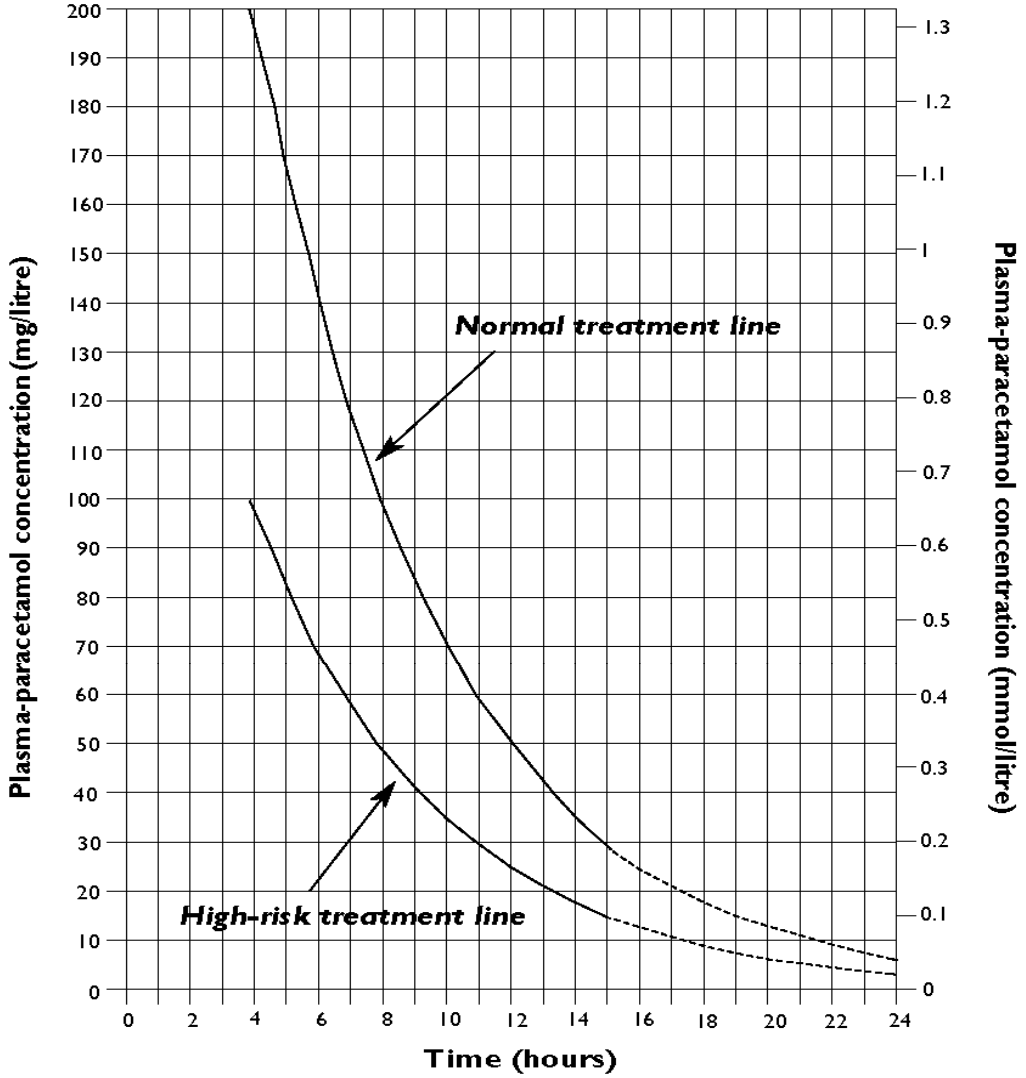
risk factor. Taking paracetamol even just above daily recommended doses (4g) following a period of fasting may cause hepatotoxicity [71].

The risk of clinically significant hepatotoxicity following paracetamol poisoning can be predicted by measurement of plasma concentration of paracetamol at a timed interval after poisoning, providing that this time interval is not less than 4 hours. The concentration is plotted on a paracetamol treatment graph with a reference line ('normal treatment line') joining plots of 200 mg/l (1.32 mmol/l) at 4 hours and 6.25 mg/litre (0.04 mmol/litre) at 24 hour [31] (Figure 1.2). Patients whose plasma paracetamol concentrations are above the "normal treatment line" or "high risk line" in the high risk group are treated with IV NAC.

1-2-3-2-3: Effect of paracetamol on clotting factors

Previous studies have shown that at therapeutic doses paracetamol decreases prothrombin index and increases international normalised ratio (INR). The early case reports began to appear in the literature in 1968 indicating an interaction between coumarin anticoagulants and paracetamol [72], however, supporting scientific evidence was only published in 1998 [73]. The study initially investigating risk factors of excessive warfarin anticoagulation in a clinical setting reported that paracetamol ingestion was independently in a dose-dependent manner associated with high INR greater than 6.

Figure 1.2: Nomogram used for treatment of paracetamol poisoning in the UK (from [31])



Patients whose plasma-paracetamol concentrations are above the **normal treatment line** should be treated with acetylcysteine by intravenous infusion (or, if acetylcysteine cannot be used, with methionine by mouth, provided the overdose has been taken **within 10–12 hours** and the patient is not vomiting).

Patients on enzyme-inducing drugs (e.g. carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, alcohol, and St John's wort) or who are malnourished (e.g. in anorexia, in alcoholism, or those who are HIV-positive) should be treated if their plasma-paracetamol concentration is above the **high-risk treatment line**.

The prognostic accuracy after 15 hours is uncertain but a plasma-paracetamol concentration above the relevant treatment line should be regarded as carrying a serious risk of liver damage.

Graph reproduced courtesy of University of Wales College of Medicine Therapeutics and Toxicology Centre

Further studies showed that paracetamol increases INR in patients on warfarin [74;75] and suppress vitamin K-dependent clotting factors (II, VII, IX, X) , supporting the existence of clinically significant interaction between Warfarin and daily dose of paracetamol (2-4g) [74-78].The exact mechanism of the interaction is not known, but the most plausible hypothesis is that paracetamol or its metabolites interfere with enzymes involved in vitamin K-dependent coagulation factor synthesis. Although some other studies have not shown significance interaction between paracetamol and anticoagulant therapy [79;80], the possibility of such an interaction must be considered by clinicians in clinical practice. Whether it has any relevance to the measurement of INR as a risk assessment in paracetamol overdose is less clear, but in general changes in clotting function in this situation are thought predominantly due to hepatic injury.

1-3: Paracetamol and Kidney

1-3-1: Epidemiology of Nephrotoxicity

The kidney is the second target organ in paracetamol poisoning. Renal insufficiency during the course of paracetamol overdose, with or without concomitant hepatic failure, has been reported since the1970s [42;81-90]. The incidence of paracetamol-induced renal failure varies in different studies and various conditions. It has been reported that the incidence of acute renal failure in paracetamol poisoning is less than 2% overall and 10% in severe poisoning

[18]. Before usage of NAC as a treatment of choice for paracetamol poisoning, renal failure requiring dialysis occurred in approximately 1% of unselected patients arriving to hospital following paracetamol overdose [18;91]. In another unselected patient series with later presentation (more than 10h), which included more severe toxicity, renal failure developed in 21% [90]. This figure increases to 50%-70% in patients who have concomitant liver failure [53;92].

In the following section the physiology of kidney function and pathophysiology of paracetamol-induced nephrotoxicty are reviewed.

1-3-2: Physiology of Renal function

The kidney maintains the constancy of the extracellular fluid by producing an ultrafiltrate of the plasma, free of blood cells and macromolecules, which is processed, reclaiming what the body needs, and excreting the rest as urine. Every 24 hours, an adult's kidneys filter 25000 mEq of sodium (total body sodium is ~ 1200-2800 mEq), and 180 L of water (total body water is around 25-60 L). Only 0.5% of the filtered sodium and 1% of filtered water are excreted [93].

Renal function begins with filtration at the glomerulus, which is a highly permeable capillary network between afferent and efferent arterioles. The relative constriction and dilatation of these arterioles control glomerular

filtration rate (GFR). In normal conditions, ~ 20% of the plasma water entering in the glomeruli goes through the filter, carrying with it electrolytes and small metabolites and leaving behind blood cells and larger proteins. Then, the filtrate enters a series of tubules that reabsorb most of it and secrete certain molecules such as amino acids and acids/bases into the urinary space. 60-70% of reabsorption occurs in the proximal tubules. Distal to that is loop of Henle, which controls concentration and dilution of the urine. The final part of the nephron is distal tubule, which fine-tunes the balance between excretion and reabsorption [93].

Sodium reabsorption is controlled in the proximal and distal part of the tubule. Sodium handling is regulated by hydrostatic and oncotic pressure in the peri-tubular capillaries in the proximal tubules; and by hormones such as aldosterone in the distal tubules. Water balance is principally regulated by the loop of Henle, which makes the medullary interstitium hypertonic; and by the level of anti-diuretic hormone (ADH) in the final segment of nephron (collecting duct) [93]. Sodium-potassium ATPase (NAKA), also known as sodium-potassium pump, in the loop of Henle and collecting duct excretes two potassium ions into the lumen in exchange for reabsorption of three sodium ions into the blood. The kidneys also regulate potassium and hydrogen ions, both of which are affected by aldosterone in the distal tubule [94]. The kidney also plays an important role in phosphate homeostasis [95].

1-3-2-1: Renal potassium handling

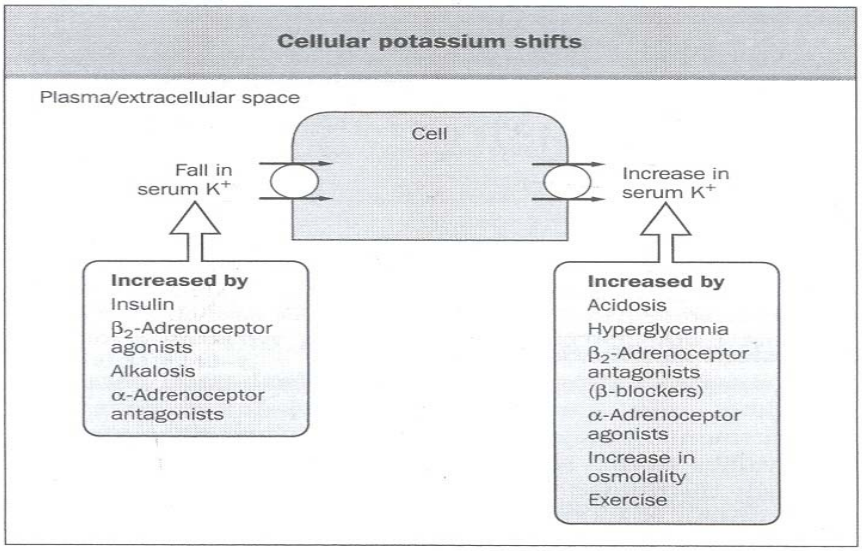
Potassium is the major intracellular cation in the human body and is involved in the regulation of intracellular enzyme function, and neuromuscular tissue excitability. The typical Western diet contains approximately 70-150 mmol potassium per day. The gastrointestinal (GI) tract absorbs potassium efficiently. After absorption from the GI tract, potassium is distributed into the intracellular (ICF) and extracellular fluid (ECF) compartments. Total ICF potassium body content is 3000-3500 mmol in healthy individuals and is primarily located in muscle (70%), with smaller amounts present in bone, red blood cells, liver, and skin (Table 1.1). Only 1-2% of the total body potassium is distributed in ECF [94]. Normally plasma potassium has narrow range of 3.5-5.5 mmol/l. The ratio of potassium concentration in ICF to ECF is a major determinant of cell membrane potential, and intracellular electro-negativity, because of action of potassium-selective ion channels. This means that a small change in extra cellular potassium concentration can cause a significant effect on neuromuscular tissue excitability. Thus, the body has developed complex regulatory mechanisms to maintain potassium homeostasis [96].

Table 1.1: Distribution of total body potassium distribution in organs and body compartments (Adapted from [94])

Distribution of total body potassium in organs and body compartments			
Organs and compartment		Body compartment concentration	
Muscle	2650 mmol	Intracellular concentration	150 mmol/L
Liver	250 mmol		
Interstitial Fluid	35 mmol	Extracellular concentration	4 mmol/L
Red Blood Cells	35 mmol		
Plasma	15 mmol		

With potassium addition to ECF, there is a concomitant shift of potassium from the ECF to ICF compartment. Conversely, in the state of potassium depletion there is a cellular potassium shift into the ECF, particularly from muscle. This process minimises changes in transcellular potassium ratio and membrane potential. Accordingly, a small change in ECF potassium concentration is often associated with significant change in total body potassium [94;96]. Short-term potassium homeostasis occurs via transcellular potassium shifts. There are several important factors that affect potassium shift between the ICF and ECF (Figure 1.3).

Figure 1.3: Regulation of extracellular and intracellular potassium (From [94])



Acidosis associated with inorganic anions such as ammonium chloride (NH_4Cl) and hydrochoric acid (HCL) result in hyperkalemia due to movement of potassium out of cells; however, acidosis associated with organic acids such as lactic acid have no significant effect on cellular shifts of potassium [97].

Insulin and ß$_2$-adrenergic receptor activation cause cellular potassium uptake by Na^+-K^+-ATPase stimulation, resulting in lower plasma potassium. In contrast, α-adrenergic receptors activation opposes the ß$_2$-adrenergic receptor effect. Exercise induces α-adrenergic receptors

activation and movement of potassium out of skeletal muscle, resulting in hyperkalemia [98].

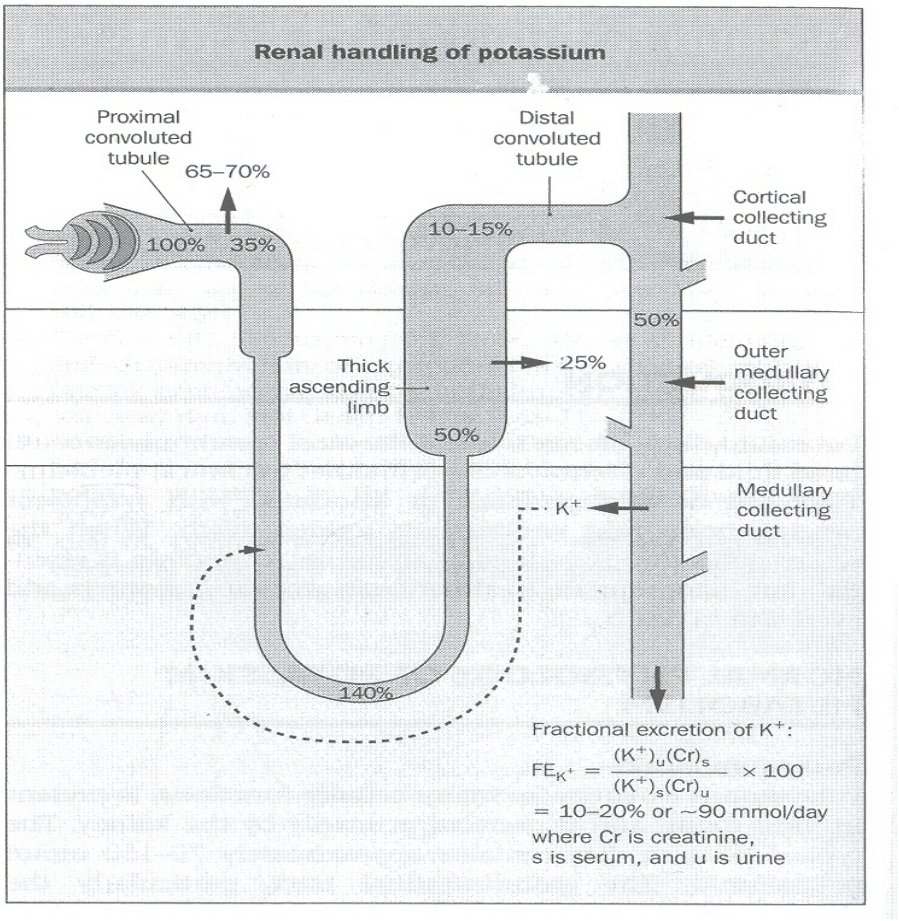
The kidney is responsible for long-term potassium homeostasis, primarily via urinary potassium excretion, which is regulated extensively by active transport in the collecting duct. Potassium is completely ionized and does not bind to plasma protein. It is therefore, filtered by the glomerulus (Figure 1.4). Proximal tubules reabsorb 60-70% of filtered potassium passively, but this segment exhibits little regulation in response to changes in dietary potassium intake.

Potassium is then secreted into tubular fluid in the descending limb of loop of Henle. The main site of active potassium reabsorption is the thick ascending limb of the loop of Henle by the action of "Na^+-K^+-$2Cl^-$ co-transporter" (Figure 1.5a). Therefore modest net reabsorption of filtered potassium usually occurs in the loop of Henle. This reabsorption can be altered to secretion by administration of a loop diuretic, or large doses of potassium loading. However, the majority of potassium excretion is normally modulated by alteration in the rates of active secretion and absorption occurring in distal convoluted tubules and collecting duct [94;96]. By the end of the distal convoluted tubule, only 10% -15% of filtered potassium remains in the tubule lumen. Net potassium transport in the collecting duct and outer medullary collecting duct occurs through

distinct cell types, named “principal cells” that allow fine regulation of renal potassium excretion (Figure 1.5b).

Several factors affect potassium secretion by principal cells. In relative order of importance, these factors are: luminal flow rate and distal sodium delivery; aldosterone, extracellular potassium and extracellular pH. An increase in luminal flow rate induces potassium secretion. In contrast, low luminal flow rate status, such as pre-renal uraemia and urinary tract obstruction, may result in reduced potassium excretion and hyperkalemia. Decreasing apical sodium reabsorption, either from reduced luminal sodium delivery or due to sodium channel inhibitors, decreases potassium secretion. Aldosterone increases Na^+-K^+-ATPase expression and thereby stimulates potassium secretion [94]. An increase in ECF potassium directly stimulates Na^+ -K^+ATPase, leading to potassium secretion.

Figure 1.4: Renal handling of potassium (from [94]



60-70%of filtered potassium is passively reclaimed by the end of the proximal convoluted tubules. Potassium is then added to tubular fluid in the descending limb of loop of Henle. The main site of active potassium reabsorption is the thick ascending limb of the loop of Henle, so that, by the end of the distal convoluted tubule only 10% -15% of filtered potassium remains in the tubule lumen. Potassium is secreted mainly by the principal cells of the cortical collecting duct and outer medullary collecting duct. Potassium reabsorption occurs via the intercalated cells of the medullary collecting duct. Urinary potassium excretion is the result of difference between potassium secreted, and potassium reabsorbed [94;99;100].

Figure 1.5a: Mechanism of potassium reabsorption in the thick ascending loop of Henle (from [94]).

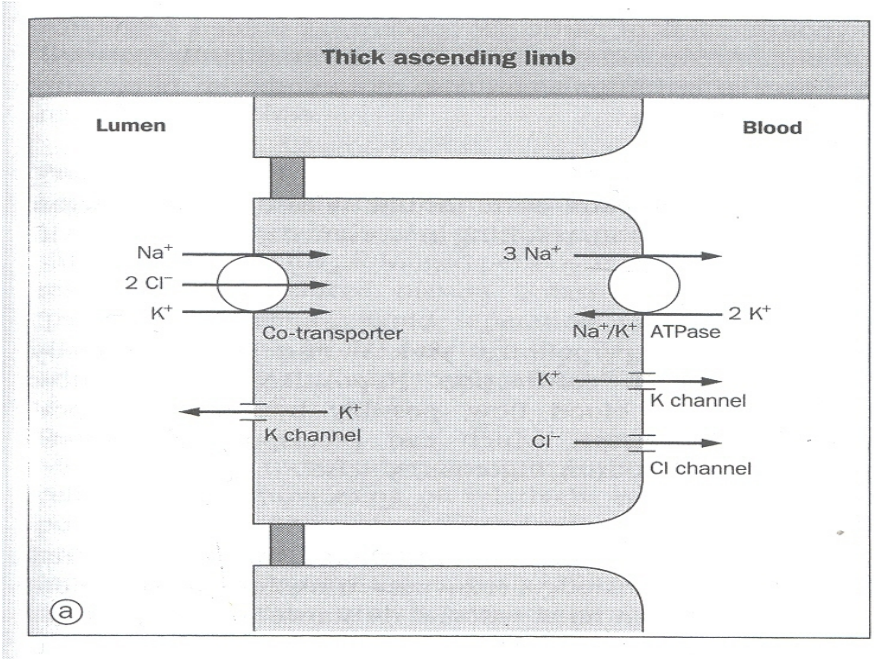
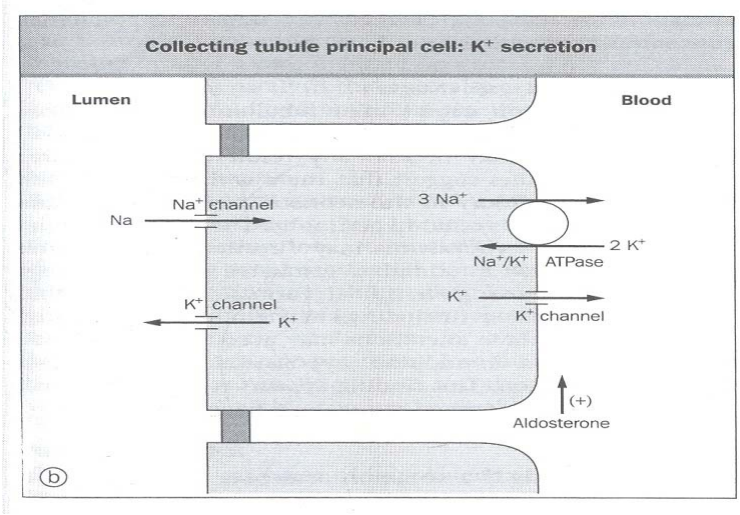


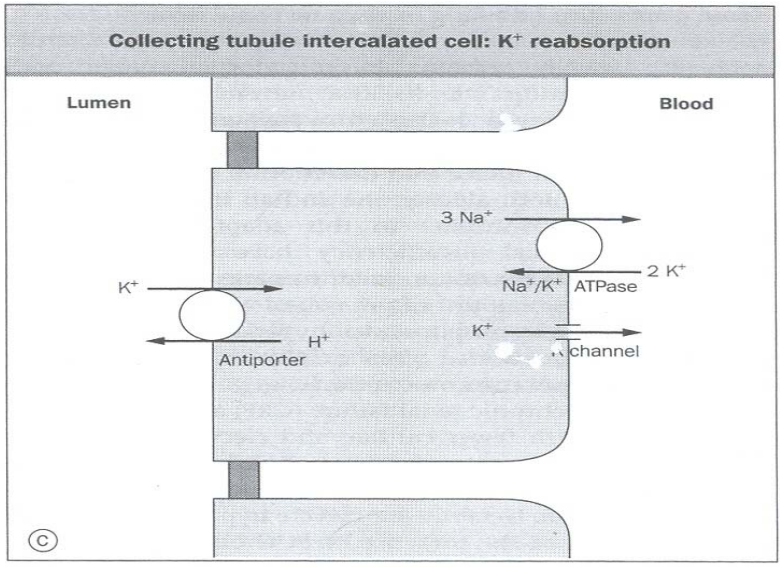
Figure 1.5b: Mechanism of potassium secretion in collecting tubules (from [94])



Finally metabolic acidosis decreases potassium secretion through a direct effect on potassium channels, and also through changes in interstitial ammonia concentration [101]. Reabsorption of potassium in the medullary collecting duct occurs through the action of the intercalated cell (Figure 1.5c).

Intercalated cells reabsorb potassium via H^+-K^+-ATPase which actively secretes hydrogen ions [H^+] into luminal fluid in exchange for reabsorbed potassium. In the status of severe potassium depletion, by this mechanism, the kidney reduces potassium excretion to 15 mmol or less daily [94;96;102].

Figure 1.5c: Mechanism of potassium reabsorption in collecting tubules (from [94])



1-3-2-2: Renal handling of phosphate

The physiological concentration of plasma phosphate in normal adults ranges from 0.80–1.44 mmol/l (2.5-4.5 mg/dl), and 80 to 85% of the total body phosphate is found in the skeleton. The rest is widely distributed throughout the body in the form of organic phosphate compounds. In the extracellular fluid phosphate is present mostly in the inorganic form, with over 85% of plasma phosphate present as the free ion, the rest being protein-bound. Phosphate plays an important role in several aspects of cellular metabolism [95]. Dietary intake and GI absorption of phosphate, urinary excretion of phosphate, and shifts between the ICF and ECF are major determinants of plasma concentration. Abnormalities in any of these steps can cause either hypo- or hyperphosphatemia [95;103].

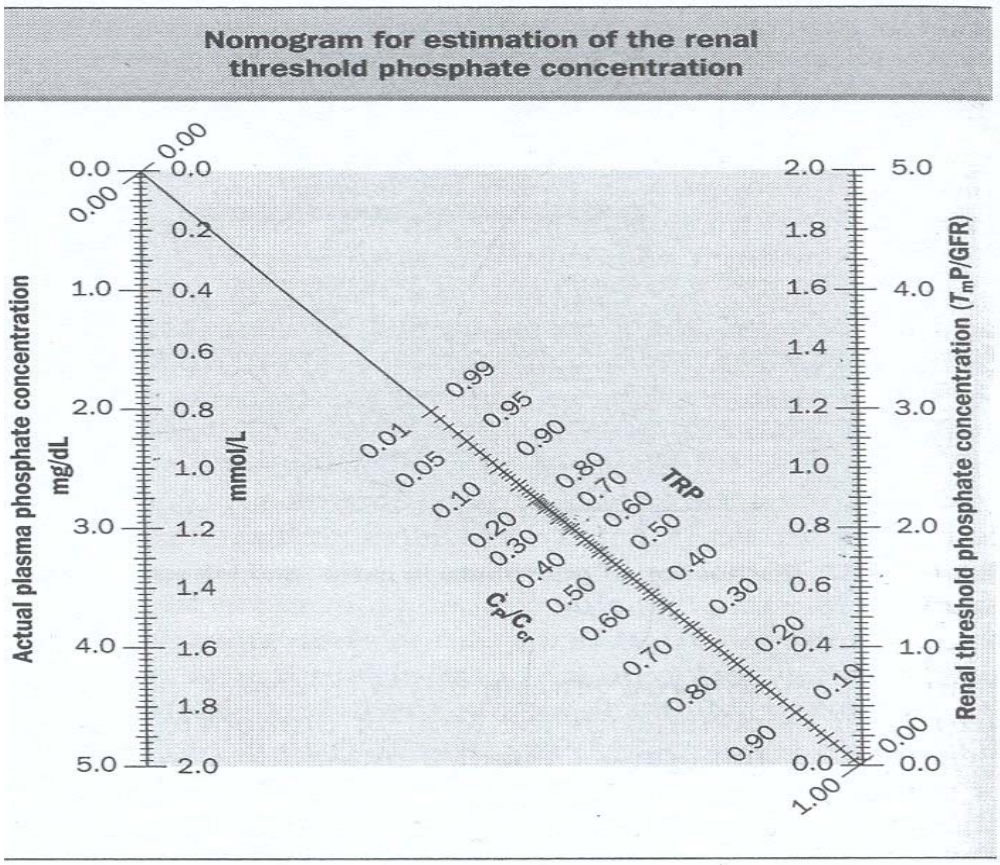
The kidneys play a major role in regulating ECF phosphate homeostasis [104]. Under normal conditions, the daily amount of phosphate which is excreted in the urine equals that absorbed in the intestine. This comprises 5-20% of filtered phosphate. The amount of phosphate which is reabsorbed can be expressed in relation to the amount filtered as TRP (total reabsorbed phosphate). TRP is calculated from:

$$[1- (Cl_p / GFR)] * 100 \text{ or } 1- [(U_p * P_{Cr}) / (P_p * U_{Cr})]$$

Phosphate clearance (Cl_p), urinary phosphate (U_p) and plasma phosphate (P_p) can all be measured and related to urinary (U_{Cr}) and plasma creatinine. The maximal TRP corrected for GFR is called renal threshold phosphate concentration (T_m P/GFR) or Bijvoet index [103]. This index represents the concentration above which most phosphate is excreted, and below which most reabsorbed. This can be estimated from plasma phosphate concentration, and TRP (Figure 1.6).

After passing through the glomerulus, part of the filtered phosphate is reabsorbed by the tubules, according to the body's need. The majority of phosphate (55-75%) is reabsorbed in the proximal convoluted tubules by way of a sodium gradient-dependent process (Na-Pi co transport) located on the apical brush border membrane. Recently two distinct Na-Pi co-transporter proteins have been cloned from the kidney (type I and type II Na-Pi co-transporter proteins) [105;106]. Urinary excretion of phosphate is modulated by a large number of endocrine and metabolic factors, most of which, including alterations in dietary phosphate content and parathyroid hormone, have been shown to modulate the proximal tubular apical membrane expression of the type II Na-Pi co-transporter protein [95].

Figure 1.6: Nomogram for the estimation of renal threshold phosphate concentration (T_m P/GFR).



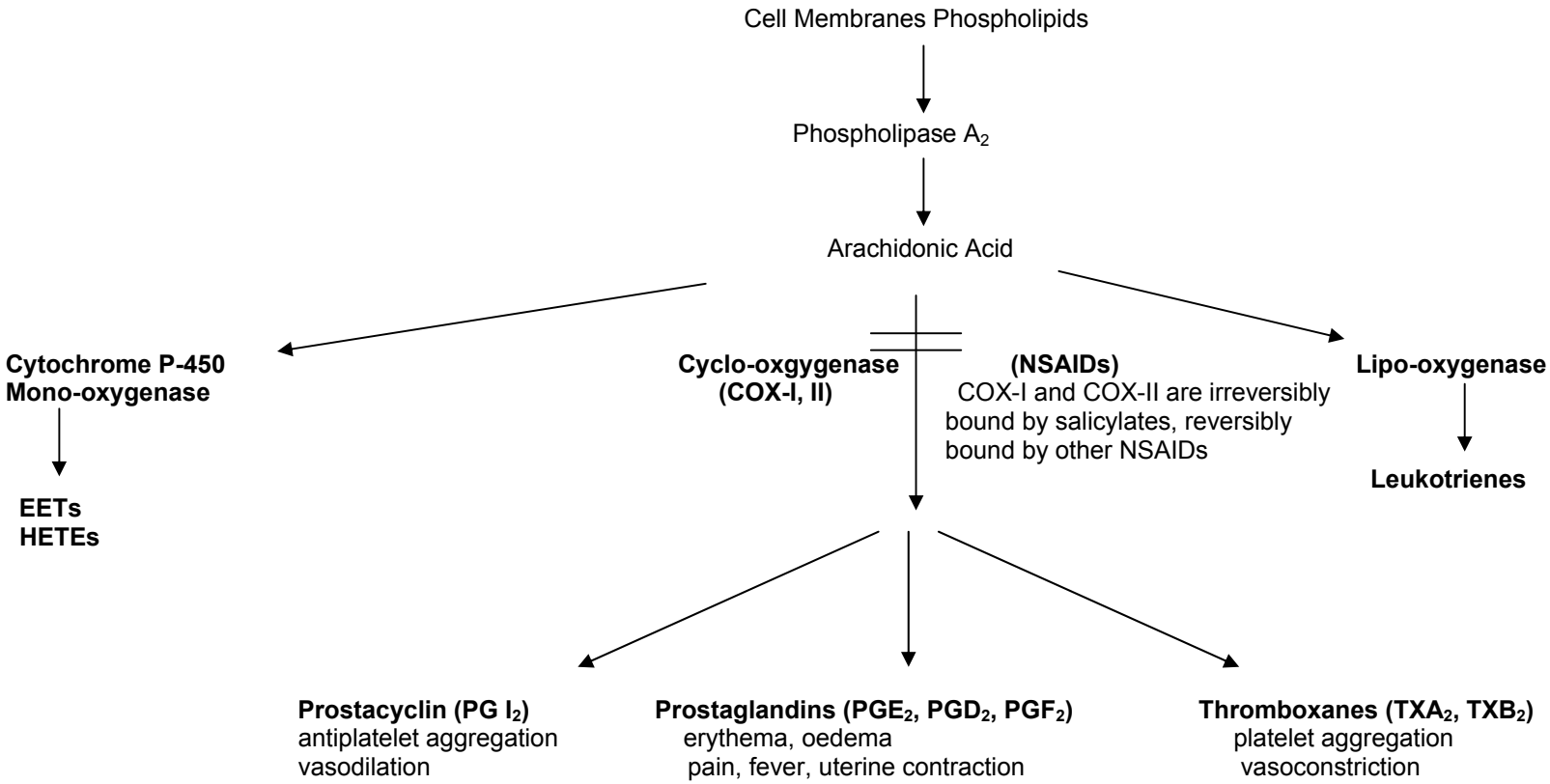
A straight line through the appropriate values of plasma phosphate concentration and TRP or Cl_p / Cl_{Cr} where Cl is clearance for phosphate (p) and creatinine (Cr) passes through the corresponding value of renal threshold phosphate concentration (T_m P/GFR) (from [103]).

1-3-2-3: Nephron structure and functional significance of renal prostaglandins

Prostaglandins (PGs), prostacyclin and thromboxanes (TX), family of 20-carbon fatty acids, are synthesised from arachidonic acid in the renal tissues (Figure 1.7). PGs have vasodilatory effects and are essential for the maintenance of renal perfusion. If there is reduction in actual, or effective, circulating volume, they influence water and electrolyte homeostasis (Table 1.2). The anatomical sites of production of PGs and their metabolites affect their main activity [107;108]. Thus PGI_2 is mainly found in the glomerulus and is the primary PG that influences glomerular hemodynamics [107;109].

Although certain endothelial-derived autacoids such as nitric oxide and endothelin-1 balance renal perfusion in both disease and health, PGs have minor effects on renal hemodynamics in healthy individuals. However, in low renal perfusion states, renal vasodilation is dependent to the presence of PGs. Administration of NSAIDs which have inhibitory effects on PG synthesis in such circumstances can decrease renal plasma flow and glomerular filtration rate (GFR), resulting in an hypoxic insult to the kidney [110].

Figure 1.7: Metabolic pathway of arachidonic acid cascade (Adapted from [110;111])



EETs: epoxyeicosatrienoic acids; HETEs: hydroxyeicosatetraenoic acids; PG: prostaglandin; TX: thromboxane

Table 1.2: Effects of renal autacoids in the kidney (Adapted from [110])

Location	Autacoid	Response
Glomerular Arterioles		
Afferent	PGI_2 *	Dilation
	PGE_2	Dilation
Efferent	PGI_2	Dilation
Capillary tuft	PGI_2	Dilation
Glomerular Mesangium	PGI_2	Relaxation
	PGE_2	Relaxation
	TXA_2 **	Contraction
Proximal tubule (S_1 segment)	5, 6-EET +	Inhibition of Na^+-K^+-ATPase
	12 (R)-HETE ++	
	20-HETE	
Loop of Henle		
Thin segment	none	-
Thick ascending limb	5, 6-EET	Inhibition of Na^+-K^+ ATPase
	12 (R) - HETE	
	20-HETE	
	PGE_2	
	PGG_2	
	PGH_2	
Distal tubule	none-low PGE_2	-
Juxtaglomerular Apparatus	12 (R) - HETE	Renin releases
	PGI_2	
Collecting tubule, interstitium, and	PGE_2	Inhibition of ADH or AVP
Vasa Recta	12-(R)- HETE	Vasodilation
	PGE_2	

PG: prostaglandin *
TX: thromboxane **
EETs: epoxyeicosatrienoic acids +
HETEs: hydroxyeicosatetraenoic acids ++

The net effect of PGs on renal hemodynamics is the result of interactions with a number of other vasoactive compounds in the kidney vasculature. While angiotensin II (AII) has minor effects on the afferent arterioles, or within the capillaries of the glomerulus, efferent arterioles are extremely sensitive to the effect of AII. The vasoconstrictive effects of AII are counterbalanced mainly by PGI_2 and to a lesser extent by PGE_2 [108;109]. Renin release is also controlled partially by PGI_2 [107;108]. Inhibition of PG production by administration of NSAIDs can, therefore, affect the renin-angiotensin-aldosterone system, resulting in hyporeninemic hypoaldosteronism, hyperkalaemia and hyponatremia [110;112;113], in particular in patients with pre-existing renal impairment. PGE_2 is the main PG produced in the collecting tubules and interstitium. It is the primary PG that influences medullary hemodynamics, and sodium and water handling [107;108] (Table 1.2).

PGs have natriuretic effects via two mechanisms: first PGs cause vasodilation and increase renal blood flow and subsequently a reduction in proximal reabsorption of sodium; secondly, PGs directly inhibit sodium reabsorption at the thick ascending limb of the loop of Henle. Thus, administration of NSAIDs can cause sodium retention and reduce response to diuretics [110;114].

Cytochrome P-450 metabolites of arachidonic acid (HETEs: hydroxyeicosatetraenoic acids and EETs: epoxyeicosatrienoic acids) (Figure 1.7) are also natriuretic. They are mainly found in the proximal tubules and the medullary thick ascending limb of the loop of Henle (Table 1.2). The primary effect of HETEs is inhibition of "Na^+ - K^+ - ATPase" at the S1 segment of proximal tubules and medullary thick ascending limb, and possibly vasodilation of the medullary capillary plexus [110;114].

The enzyme responsible for PG synthesis is cyclo-oxygenase which has two isoenzymes known as COX-I and COX-II (Figure 1.7). Both isoenzymes are expressed in the kidney. COX-I, which is a constitutive enzyme, is expressed in most cells, including platelets. It is involved in tissue homeostasis and cell-cell signalling and its inhibition is associated with GI bleeding and ulceration. COX-II produces prostanoid mediators in inflammatory reactions. The pharmacological effects of some drugs such as NSAIDs are due to inhibition of COX-I and COX-II. Most NSAIDs currently being used are inhibitors of both isoenzymes and their unwanted effects are primarily associated with the inhibition of COX-I. New NSAIDs which selectively inhibit COX-II have come on the market, based on the hypothesis that by inhibiting only COX-II these agents can be as efficacious as nonselective NSAIDs, but with less GI effects. However, further studies showed that COX-II inhibitors exhibit the same renal effects as non selective NSAIDs. Findings of studies conducted on rofecoxib

showed that COX-II is constitutively expressed in the human kidney and contributes to production of renal PGs. Thus renal function may be adversely affected due to vasoconstriction following NSAID-induced COX-II inhibition and therefore PG synthesis inhibition, particularly in people with underlying renal disease. Rofecoxib and valdecoxib are potent and selective COX-II inhibitors [111;115;116] and cases of acute renal failure (ARF) associated with the use of both these agents have been reported [115-117].

1-3-3: Pathophysiology of Nephrotoxicity

The kidneys are susceptible to toxic or ischemic injury for five important reasons:

1: while the kidneys make up less than 1% of total body, they receive 20-25% of cardiac output;

2: because of high metabolic activity (enzyme systems and transcellular transport), they are susceptible to agents that disrupt metabolism;

3: their ability to remove water from filtrate results in a high concentration of toxic substances in the medulla which is harmful to the kidney;

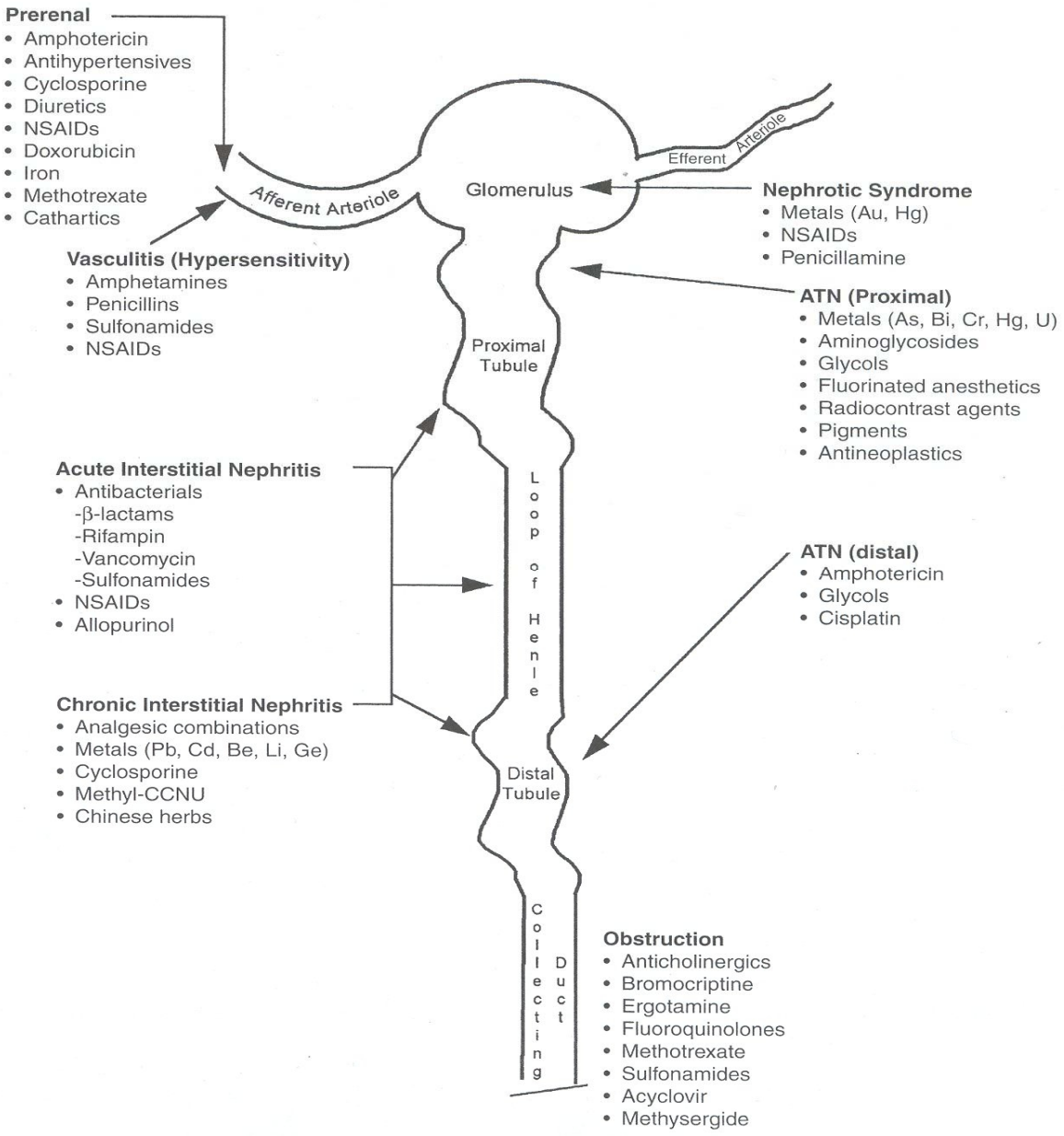
4: they have the largest endothelial surface by weight;

5: they alter tubular fluid acidification and this in turn influences plasma protein binding.

All these factors may be affected by toxins [118;119].

Injury to any part of the nephron, either glomeruli or tubules, can cause renal dysfunction and therefore decrease in GFR and increase in plasma levels of the marker substances urea and creatinine. However, the relationship between GFR and urea and creatinine is hyperbolic not linear, meaning that a small increase in plasma level of these markers denotes a significant renal dysfunction. By the time plasma creatinine exceeds the normal range, GFR is already reduced by greater than 50% [93]. While nephrotoxins may influence any segment of the nephron they usually affect the tubules, the most metabolically active segment of the nephron. Glomerular damage may also result from drugs or chemicals. These processes are not mutually exclusive, and toxic nephropathy may involve more than one part of the nephron (e.g. NSAID-induced ARF and nephrotic syndrome) [93;118;120] (Figure 1.8).

Figure 1.8: Major nephrotoxic processes and the sites of injury induced by nephrotoxic agents (from [93])



1-3-4: Acute renal failure (ARF)

ARF is characterized by a sudden decline (hours to days) in renal function sufficient to decrease the elimination of urea and creatinine and other uraemic toxins [121]. The true incidence of ARF is difficult to determine from the literature because of the wide variation in the populations studied, and different diagnostic criteria for the definition of ARF. It is generally believed that the incidence of ARF in the hospital setting is approximately 5% in all patients, and 15-25% in the critically ill patients [122]. ARF can result from low renal perfusion without cellular injury; an ischemic, toxic or obstructive insult to the tubules; a tubulointerstitial process with inflammation and oedema; or a primary reduction in the filtering capacity of the glomerulus.

Traditionally, ARF is classified into three pathophysiological processes: pre-renal, intrinsic and post-renal failure. If tubular and glomerular function is intact, but, renal function is affected by factors compromising renal perfusion, the failure is called “pre-renal”. If the renal dysfunction is caused by an obstruction of the urinary outflow tract, it is defined as “post-renal” failure; and if the primary source of failure is intra-renal it is termed “intrinsic” renal failure. Pre-renal and intrinsic renal failure due to ischemic and nephrotoxic insults are the most common causes of ARF [123].

1-3-4-1: Pre-renal ARF

Pre-renal ARF is responsible for approximately 70% of community-acquired [124] and 40% of hospital-acquired ARF cases [125]. Sustained hypo-perfusion is the most important predisposing factor for ischemia-induced tubular necrosis. Pre-renal ARF in the poisoned patient can occur from mechanisms leading to hypotension and subsequently renal hypo-perfusion. These mechanisms include: cardiotoxicity leading to a lower cardiac output, vasodilation, vasoconstriction and loss of effective circulatory volume due to diuresis, GI fluid loss, bleeding, or third space volume such as in a chemical burn.

Nephrotoxins may produce pre-renal failure by affecting the intra-renal vasculature, leading to decreased renal blood flow and GFR. Renal blood flow is a result of a balance between vasoconstrictors (catecholamines, A II) and vasodilator (PG) factors. Some toxins such as NSAIDs inhibit the formation of the vasodilatory PGs, causing vasoconstriction. This effect, at therapeutic doses of NSAIDs, generally does not compromise renal function, however, in hypo-perfusion states, such as volume loss, shock or congestive heart failure, it may precipitate ARF. Elderly patients are particularly susceptible to pre-renal ARF [118;123].

1-3-5: Risk factors and Mortality of ARF

Risk factors of ARF can be patient related or drug/toxin related (Table 1.3). In pre-renal uraemia renal injury is more likely to occur after drugs that alter intra-renal haemodynamics, such as NSAIDs [126;127], or reach high concentration in the renal tissue, such as aminoglycosides [128]. Aminoglycosides are renally excreted and therefore accumulate more easily in ARF, and then are concentrated in the kidney and cause injury. Patients with a history of renal disease are more susceptible to the nephrotoxic drugs [129;130]. Age is also an important risk factor. Elderly patients are more likely to develop ARF and have a poor prognosis because of the structural change (reduction in renal size and volume, reduction in the number of glomeruls, change in the renal tubules, interestitium and renal vessels) and functional changes (reduction in renal plasma flow and to lesser extent in GFR) observed in the aging kidney [131-133]. Liver disease has been shown to increase the risk of ARF and mortality [134]. Patients with non-oliguric renal failure (urinary output ≥ 400 ml per day) have a better prognosis [135].

Dialysis requirement in patients with ARF ranges from 20-60%. Less than 25% of those who survive initial dialysis require long-term dialysis. This indicates the potential reversibility of the syndrome [123]. Mortality rate in ARF ranges from 7-100% in different population studied. The mortality rate

of patients admitted to hospital with pre-renal uraemia has been reported as 7% [124]. This increases to 50-100% in patients with post-operative ARF [136;137]. In this group of patients ARF will occur largely in the setting of multi-organ failure.

Table 1.3: Risk factors for Renal Failure (Adapted from [138]

Patient-related Risk Factors

- Age, Sex
- Previous renal insufficiency
- Specific disease (diabetes mellitus, multiple myeloma, those associated with proteinuria, lupus)
- Sodium-retaining states (cirrhosis, heart failure)
- Dehydration and volume depletion
- Hyperuricemia, hyperuricosuria)
- Sepsis, shock
- Renal transplantation

Drug-related Risk Factors

- Inherent nephrotoxic potential
- Dose
- Duration, frequency, and form of administration
- Repeated exposure

1-3-6: Laboratory Examinations and Disturbances in ARF

1-3-6-2: Plasma creatinine

Detection of changes in plasma creatinine and urea have long been used as conventional surrogate markers for the diagnosis and classification of acute renal failure. However, theses markers have some limitations since neither

reflect time-course of changes in GFR. These markers require some time to accumulate before being detected in plasma as abnormal, and this potentially results in a delay in the diagnosis of the renal dysfunction. Production and release of creatinine into plasma can be highly variable. Some factors including age, sex, muscle mass (i.e., neuromuscular disease, malnutrition, amputation), dietary intake and drugs (e.g., trimethoprim, cimetidine) may affect creatinine production and excretion. Moreover, 10-40% of creatinine is excreted by tubular secretion and this has the potential to hide a significant initial decline in GFR [139]. Nevertheless serum creatinine is still widely used as a surrogate marker of renal function by clinicians worldwide, primarily due to simplicity, familiarity and low cost.

1-3-6-2: Hypokalaemia

Hypokalaemia is a common electrolyte abnormality in hospitalised patients. It is usually defined as plasma potassium of less than 3.5 mmol/l. Patients with mild hypokalaemia (plasma potassium concentration 3.0- 3.5 mmol/l) usually have no symptoms. However, patients with more severe hypokalaemia (plasma potassium concentration of less than 2.5 mmol/l) may develop generalised weakness, muscle necrosis (rhabdomyolysis) and paralysis [140-142]. Both mild and severe hypokalaemia increase risk of cardiac arrhythmias [143;144]. Hypokalemia also has some other effects including, hormonal, muscular and

renal effect [94]. Hypokalemia can be classified in five groups: pseudohypokalemia; redistribution or transcellular shift; hormonal imbalance, renal potassium loss and other causes.

Pseudohypokalemia: large number of white blood cells in certain disease states, such as acute myelogenous leukaemia, when stored for a long period at room temperature can take up extracellular potassium resulting in low potassium concentration in the laboratory [94].

Redistribution: more than 98% of total body potassium is located in ICF. Therefore, movement of small amount of potassium from ECF to ICF can alter plasma potassium concentration markedly. As discussed earlier many hormones (insulin, glucagon and aldosterone), $ß_2$-adrenergic agonist, and plasma acid-base changes stimulate cellular potassium uptake, resulting in hypokalemia [94;97;141;145].

Hormonal imbalance: aldosterone is the most important hormone regulating total body potassium homeostasis, resulting in hypokalaemia both by inducing potassium uptake into cells, and by increasing potassium excretion [94;141]. Any disorder that affects aldosterone synthesis can also alter potassium haemostasis [146-148].

Renal potassium loss: renal potassium loss is the most common cause of hypokalaemia either due to medications, endogenous hormone production, or rarely due to intrinsic kidney disease (eg. Bartters's, Gitelman's syndrome, Liddle's syndrome). Both thiazide and loop diuretics induce urinary potassium excretion in a dose-dependent and treatment duration-related manner [94;149;150]. Certain antibiotics such as penicillins [151], aminoglycosides [152], and antifungal agents [153] increase renal potassium loss. There have been reports of hypokalaemia associated with anticancer drugs such as cisplatin [154;155]. Toluene exposure from sniffing certain glues can also cause renal tubular acidosis and renal potassium loss [156].

Other causes: magnesium deficiency can cause renal potassium wasting. This condition should be considered in any adult patient with hypokalaemia of unknown aetiology [157;158]. Any case of increase in distal tubular bicarbonate delivery, such as metabolic alkalosis, renal tubular acidosis or treatment of renal tubular acidosis can also increase potassium secretion [94]. Hypokalaemia, although less frequent, may develop in excessive sweating, chronic diarrhoea, vomiting, or prolonged nasogastric suction; however, the main mechanism of potassium loss in such circumstances is renal loss due to metabolic alkalosis and hyperaldosteronism secondary to volume loss [159].

1-3-6-3: Fraction of excretion of filtered electrolytes

The fractional excretion of filtered sodium (Fe_{Na}) can help us to differentiate between pre-renal and intrinsic renal failure. Fe_{Na} is calculated from:

$$Fe_{Na} = (U_{Na} / P_{Na}) \div (U_{Cr} / P_{Cr}) \times 100$$

Fe_{Na} less than 1% is characteristic of pre-renal failure whereas value more than 1% indicates with acute intrinsic renal failure [93].

1-3-6-4: Trans-tubular potassium gradient

Trans-tubular potassium gradient (TTKG) is another useful marker of renal function. TTKG is a measurement of net K secretion in the distal nephron and corrects the urinary potassium for changes in osmolarity that may occur with water reabsorption in the collecting duct. TTKG provides an indirect measurement of the net potassium secretion of the distal tubules. It is calculated from:

$$TTKG = (U_K / P_K) \div (U_{osm} / P_{osm})$$

where U_K and P_K are the concentration of potassium in urine and plasma, respectively, and U_{osm} and P_{osm} are the osmolalities of urine and plasma, respectively.

TTKG is often used to determine if hyperkalaemia is caused by aldosterone deficiency / resistance or secondary to non-renal causes. A

value of less than 5-7 in the setting of hyperkalaemia implies impaired distal tubular secretion of potassium due to either aldosterone deficiency or resistance. A value of more than 10 indicates increased K intake and normal distal nephron handling of potassium [94].

1-3-6-5: Proteinuria and enzymuria

The kidney includes several enzyme systems, found only in specific segments of the nephron. Several different tests are being developed (enzymuria, renal tubular antigens, to screen for preclinical renal damage. The sensitivity and specificity as well as the potential clinical uses of these tests remain to be clarified. Additional application of enzymuria tests may include a role in localization of site of injury in the nephron. The anatomical site of nephrotoxicity may generally be localized by classifying proteinuria as either low molecular weight or high molecular weight. Low molecular weight proteins such as β2 microglobulin or retinol binding protein, are freely filtered at the glomerulus and are taken up by the proximal tubular cells, where they are catabolised. Thus, low molecular weight proteinuria is a highly sensitive index of proximal tubular dysfunction. In contrast, high molecular weight proteins such as albumin are repelled from glomerular filtration because of size and charge restraints. Nephrotoxins that produce a loss of glomerular size selectivity or a loss of the glomerular poly-anion can cause albuminuria. The Tamm-Horsfall is a specific renal protein

located in the thick ascending limb of the loop of Henle. It is a high molecular weight protein, and its excretion in the urine increases when this segment of the loop of Henle is damaged by toxic agent [93;160].

1-3-7: Paracetamol-induced nephrotoxicity

1-3-7-1: Pathophysiology

The mechanism of paracetamol-induced nephrotoxicity is not fully understood. Several mechanisms have been suggested. The primary pathological lesion is acute tubular necrosis which most often occurs in the context of liver injury [83;92]. However, it also occurs rarely in the absence of clinical and biochemical evidence of major liver injury [85;90;161]. Evidences of coagulative necrosis of the proximal tubular cells, tubular dilation, collection of cellular debris within damaged tubules, rupture of tubular membranes, interstitial oedema and infiltration with lymphocytes and plasma cells have been shown in the renal biopsies and autopsy specimens of patients who developed renal failure following paracetamol overdose [162-165]. Interstitial nephritis [166] and distal tubular damage [84] have also been reported.

Like liver damage, the pathophysiology of renal necrosis after acute paracetamol overdose is believed mainly due to formation of NAPQI by P450 enzymes in the renal parenchyma [18;167;168]. It is likely that the nephrotoxic

agent is the quinoneimine metabolite [169]. Further studies indicate that the quinoneimine intermediate conjugates with sulphydryl-containing macromolecules to cause renal injury [170;171]. While GSH-conjugation is primarily considered as a detoxification pathway, experimental studies have shown that GSH conjugates of paracetamol metabolism may contribute to nephrotoxicity [172]. How the binding of NAPQI-cysteine protein then causes renal damage is still not clear. In 1991 Moller-Hartmann and Sieger suggested that the mechanism of nephrotoxicity is quite different than that of hepatotoxicity in paracetamol overdose, and that paracetamol-S-conjugates might be responsible for the nephrotoxic effect of paracetamol [173]. In animal models pretreatment with either inhibitors of GGT (gamma glutamyl trans peptidase) or the probenecid-sensitive organic anion transporter prevented paracetamol-induced nephrotoxicity [174;175]. GGT catalyses the initial step in the catabolism of GSH conjugates and plays an important roles in the exposure of intracellular cells to potentially toxic S-conjugates [176]. One recent experimental study suggested a contributory role for paracetamol-GSH-derived metabolites in paracetamol-induced renal, as opposed to hepatic injury, that involved renal-selective GSH depletion [172]. Acute necrosis in the proximal convoluted tubules of the inner renal cortex of the rat was described by Mitchell et al. [168] after single non-lethal doses of paracetamol in 1977. They showed a positive correlation between renal injury and degree of covalently bound paracetamol in the renal cortex, and also described a negative correlation to renal glutathione supply. They suggested that paracetamol is converted to a

toxic metabolite by P450 enzyme within the kidney, and that glutathione protects against renal damage, in a manner parallel to the liver.

Why the occurrence of renal injury after acute paracetamol overdose is uncommon and why some patients are more susceptible to nephrotoxicity is not fully understood. This might be due to individual differences in the amount of P450 oxidases present in the kidney [164]. An additional factor might be the inducibility of oxidative enzyme system. This has been well described in the literature [30;177;178]. There are reports of sex differences in susceptibility to paracetamol-induced nephrotoxicity in animals [179-181]. Some experimental studies have shown that paracetamol-induced nephrotoxicty is more common in males [179;180]. The studies suggested that testosterone increases CYP2E1 activity in the kidney. CYP2E1 is thought to play an important role in the metabolic bioactivation of paracetamol resulting in nephrotoxicty. Other contributing factors to nephrotoxicity of paracetamol include volume depletion, hepatorenal syndrome, pre-existing renal disease, chronic excessive dosing of paracetamol, and co-ingestion with other nephrotoxic drugs [182;183].

Two clinical forms of nephrotoxicity following paracetamol overdose have been described. Within 24-48 hours oliguric renal failure develops, accompanied by proteinuria and microscopic haematuria. The oliguria usually occurs in the context of liver injury and it may last for only few hours or progress to anuria requiring haemodialysis [163;184]. The other form of renal failure with a delayed

onset is associated with hepatic failure. This form is generally accompanied by a multiple organ failure. Endotoxaemia and disseminated intravascular coagulation (DIC) have been suggested as aetiological factors in the pathogenesis of renal insufficiency [163]. Previous studies have shown that plasma renin activity (PRA), atrial natriuretic factor and aldosterone concentrations are increased in proportion to the severity of renal failure [185]. The increase in PRA is in association with renal vasoconstriction and low renal prostaglandin excretion [186].

1-3-7-2: Paracetamol and plasma electrolytes

The adverse effects of aspirin and NSAIDs on the kidney have been previously described. NSAIDs interfere with water excretion and natriuresis by PG synthesis inhibition, and, under certain conditions, may reduce renal blood flow [187]. The clinical and laboratory features of the renal effects of NSAIDs include weight gain, oedema, hyponatraemia, hyperkalaemia and interference with the effect of diuretics and antihypertensive drugs [188]. They may also cause acute renal dysfunction in patients with underlying kidney disease [189]. Furthermore, NSAIDs may cause tubulo-interstitial damage, nephrotic syndrome and renal papillary necrosis (analgesic nephropathy) [190].

Paracetamol does not seem to have renal effects similar to NSAIDs, which are associated with a more general inhibition of PG synthesis. It does not cause

clinically significant fluid and sodium retention, or renal impairment when taken in therapeutic doses [187]. Although rare, there have been reports of analgesic nephropathy with paracetamol [191].

Haylor and colleagues investigated the renal effects of acute oral administration of 1.5 g paracetamol on six healthy female subjects and showed a reduced excretion of sodium, water and PGE_2 [192]. Berg and colleagues studied the acute effect of paracetamol (40 mg/kg/day for 3 days) on renal function and PG synthesis. They reported that oral treatment with paracetamol in therapeutic doses reversibly reduced thromboxane B_2 (TXB_2), a potent vasoconstictor, for at least 4h after ingestion both in healthy controls and in patients with impaired renal function. The study also showed a reduction in PGE_2 excretion, a potent vasodilator, especially in patients with renal dysfunction, but with no significant effect on GFR or plasma electrolytes [193]. Prescott and colleagues, in a study on 10 female healthy volunteers given therapeutic dose of paracetamol, (4g daily), indometacin (150 mg daily) and placebo for 3 days, showed paracetamol and indometacin had no significant effect of GFR and effective renal plasma flow as measured by the renal clearance of inulin, creatinine and PAH (p-aminohippuric acid) [187]. However, paracetamol, and in particular indometacin, did reduce urinary excretion of PGE_2. The low urinary excretion of PGE_2 induced by paracetamol and indometacin was associated with a reduction in urinary excretion of sodium and volume retention.

Paracetamol acts differently when it is taken in overdose. An animal study [194] in which different single toxic doses of paracetamol were given to Wistar rats showed a dose dependent reduction in GFR and renal blood flow (RBF). Thereafter distal tubular damage was observed, as detected by alteration in renal concentration ability. The time course of this change after a single toxic dose of paracetamol (1000 mg/kg) was for an increase in fraction of excretion of potassium (FeK) and sodium (FeNa) to reach maximum at 16 hours after exposure. FeK and FeNa returned to normal by 24 hours. The authors concluded that the early stage of paracetamol nephrotoxicity might be due to renal hemodynamic change which may cause tubular dysfunction mainly in the distal parts of the medullary tissue. These changes occurred at different doses of paracetamol from those usually associated with a reduction in hepatic glutathione levels. Renal glutathione reduced only at high doses of paracetamol (1000 mg/kg). In this study renal damage occurred in the presence or absence of liver damage.

Hypophosphataemia is also a recognised feature of liver failure [195;196] and if severe may contribute to the morbidity and mortality by causing mental confusion, irritability, coma, blood abnormalities and rhabdomyolysis [197]. It has also been described as a general feature of paracetamol poisoning. Although the degree of hypophosphataemia is correlated with the severity of liver injury, it may also occurs in the absence of clinical or biomedical features of liver injury [198]. Several mechanisms, including systemic alkalosis, glucose

infusion during NAC therapy, the breakdown of intracellular organic phosphate in the presence of intracellular acidosis, and phosphaturia have been suggested to contribute in hypophosphataemia. However, the kidney has been suggested to play the major role in determining plasma phosphate concentration via the degree of tubular phosphate reabsorption and excretion [198-200].

A previous study on patients with paracetamol overdose showed that serum phosphate was negatively correlated with markers of liver injury, but, positively correlated with plasma potassium concentration [198]. In the same study, the renal phosphate threshold concentration (Tm PO4/GFR) was highly significantly correlated with degree of hypophosphataemia, and therefore renal loss of phosphate rather than intracellular redistribution was considered as the main cause of hypophosphataemia [198]. The authors suggested that, although renal tubular necrosis in paracetamol overdose is rare, if phosphaturia accounts for hypophosphataemia, renal tubular abnormalities appear to be far more common than previously recognised and special consideration should be given for replacement of phosphate if needed.

A further study [199] in patients with paracetamol overdose confirmed the results of the previous study [198] showing a correlation between hypophosphataemia, TmPO4/GFR, retinol binding protein (RBP), a biomarker of renal tubular damage, and severity of overdose. The authors suggested that both phosphaturia and RBP can be used as a marker of nephrotoxicity in

paracetamol overdose, however, RBP is a less sensitive marker and increases occur only in more severe cases.

1-4: Acetylcysteine (NAC)

1-4-1: NAC, the treatment of choice for paracetamol poisoning

NAC has long been used as an effective antidote in paracetamol poisoning in animals [201] and man [202;203]. NAC reduces the extent of glutathione depletion following toxic doses of paracetamol [204-206], supports the glutathione conjugation of paracetamol, and increases the urinary excretion of cysteine and mercapturic acid conjugates of paracetamol following paracetamol overdose [18;207]. High doses of paracetamol deplete inorganic sulphate and saturate sulphate conjugation. In vitro studies showed that NAC is partly metabolised to inorganic sulphates, such as sodium sulphate, and thus supports the sulphate conjugation pathway. It also increases the rate of paracetamol elimination [208;209].

The optimal route and duration of NAC administration has remained controversial. In the US a 72-hour oral regimen has long been used [210] while the current protocol for antidote therapy in paracetamol poisoning in the UK, Canada and Australia is the Prescott protocol [203], which is a step-down, 20-hour intravenous (IV) NAC infusion (150 mg / Kg over 15 min in 200 ml 5%

dextrose, followed by 50 mg/kg in 500 ml 5% dextrose over 4 hours and 100 mg/Kg in 1000 ml 5% dextrose over 16 hours). A meta-analysis has shown no difference in the outcome between oral and IV NAC regimens, however, a shorter hospital stay and the potential reduction in the bioavailability of oral NAC due to vomiting and activated charcoal administration make IV NAC regimen preferable [210]. For optimal effect it is generally accepted that NAC must be given within 10 hours of ingestion. The earlier treatment is given the more likely it is to be protective. The protective effect of NAC begins to decline after 8 to 10 hours and after 12 hours the efficacy rapidly decreases [203;211].

Patients whose plasma paracetamol concentrations are above the “normal treatment line” or “high risk treatment line” in the high risk group are treated with IV NAC (Figure 1.2). In remote areas where NAC is not available, methionine, which may be prescribed orally, can be given. Providing that the overdose has been taken within 10-12 hours and the patient is not vomiting [31].

When the time of ingestion is not known or when tablets are taken over period of several hours (staggered overdose) the plasma paracetamol concentration is difficult to interpret. In such circumstances treatment with antidote is recommended [31].

Patients who are taking P450 enzyme-inducing drugs including carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, alcohol, and St Johns Wort, or

who are malnourished (e.g. anorexia, alcoholics, or patients with malabsorption or HIV [human immunodeficiency virus] positive) may develop toxicity at a lower paracetamol concentration. In this group of patients treatment should be started when the paracetamol concentration is above the “high risk treatment line” (which is a line plotted at 50% of the normal treatment line [31] (Figure 1.2).

If patients are treated within 10 hours of overdose serious hepatotoxicity is uncommon [212]. Without treatment about 60% of patients with a plasma paracetamol concentration above the “treatment line” may develop liver injury. Of these about 5% will die [213]. The prognostic accuracy of plasma paracetamol concentration taken after 15 hours is uncertain, but a concentration above the relevant treatment line is considered as carrying a serious risk of liver injury [31]. Whether NAC treatment is beneficial in late presentation (>15 h post ingestion) and in patients with established liver failure following paracetamol overdose is less certain [214]. Studies have suggested that NAC give after 16 hours, even at the stage of encephalopathy, can improve survival [215;216]. Late NAC treatment reduced progression to grade III or IV encephalopathy and had a beneficial effect on survival even in patients with poor prognosis [215]. The main protective effects of NAC after paracetamol overdose are replenishment of reduced intracellular glutathione and detoxification on toxic metabolite; however, there are other suggested mechanisms by which NAC given in patients with later presentation could be beneficial. Experimental study has shown NAC can restore the capacity of intracellular protelolytic systems to

degrade arylated proteins [217]. Thus in vivo, poisoned cells may remain viable. Moreover, neutrophil accumulation within the liver worsens liver damage, and the antioxidant properties of NAC may prevent this [215].

1-4-2: Death from low dose paracetamol concentration

There have been reports of death and liver injury in patients with paracetamol overdose who had plasma paracetamol concentration under the treatment line and therefore, according to protocol, not treated by IV NAC [218]. While factors such as inaccurate time of ingestion, unknown number of tablets taken, staggered overdose, enhanced susceptibility to liver damage, and co-ingestion with other drugs have been suggested to be possible associated factors, recently there has been an argument regarding the accuracy of the current guideline for the treatment of paracetamol poisoning, in particular when identifying high risk patients. It has been suggested that treatment strategy must allow a margin of safety that permits some degree of inaccuracy in the patient's history or individual susceptibility to paracetamol [219]. Bridger at al suggested changing the current treatment line for use of NAC. They recommended use of a lower line passing through 150 mg/l at 4h and 30 mg/l at 12h as the standard treatment line and 100 mg/l at 4h for those patients with known risk. This standard is widely used in the US [218]. This suggestion has been discussed by others [219-226]. While some agreed with this recommendation [219;222], others questioned whether there is sufficient evidence for such a change

[220;223;225], arguing that only a small fraction of the large group of patients who have paracetamol concentration under current treatment line are at risk of paracetamol toxicity. Thus, whether using a lower treatment line can justify the increase use of in-patient resources that would be needed to treat this potentially large population is uncertain, and more information on the occurrence of death and liver failure in this group is required [225].

1-4-3: Effect of NAC on clotting factors

Antidote treatment with NAC reduces the severity of liver injury induced by paracetamol overdose [203]. Clotting factors are used as indicators of prognosis in fulminant hepatic failure [227], and management decisions in paracetamol overdose are partly based on serial measurement of prothrombin time. However, NAC itself has been shown to reduce prothrombin index in patients with paracetamol overdose [228-230] and also in healthy volunteers [229-231]. Prothrombin index measures the relative activity of clotting factor II, VII and X in comparison to normal controls. The mechanism behind anticoagulant property of NAC is unknown. It is thought that this might be due to destabilization of proteins, including clotting factors that contain disulphide bonds [232]. The results of previous studies suggest that although the prothrombin index provides useful prognostic information, management decisions should not solely rely on this value [230].

1-4-4: Anaphylaxis and anaphylactoid adverse reactions

The terms anaphylaxis and anaphylactoid reactions were first introduced by Charles Robert Richet in 1902 [233].The term anaphylaxis refers to amplified, harmful immunologic reactions that occur when the human body is exposed to a specific antigen that cross-links antigen-specific IgE molecules. These IgE molecules are bound to the surface of mast cells and peripheral basophils. This reaction leads to degranulation of mast cell and basophils resulting in immediate release of potent mediators such as histamine and tryptase. Furthermore, metabolism of arachidonic acid in cell membranes produces other mediators, including prostaglandins and leukotrienes (Figure 1.7).

The pre-formed and newly generated mediators of mast cell and basophil degranulation are responsible for the sudden and potentially life-threatening progression of events involving cardiovascular and respiratory systems, GI (gastrointestinal) tract and skin (Figure 1.9 and 1.10).

Initial anaphylactic symptoms include nasal congestion, rhinorrhea, conjunctivitis, flushing, pruritus, nausea, vomiting, diarrhoea, urinary urgency and uterine cramp. In more severe cases patients may develop hypotensive shock and cardiovascular collapse, laryngeal bronchospasm, asphyxia and death. Symptoms usually occur within 20 minutes following exposure to the

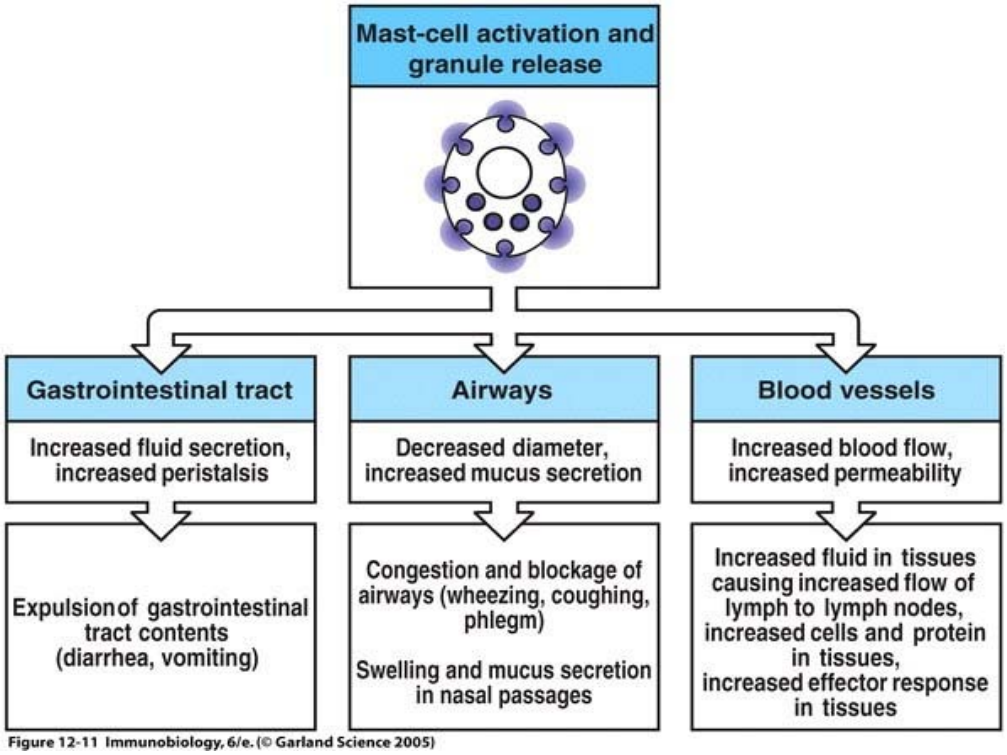
agent; however, the time course can be variable. In general, larger oral doses and IV administration are more likely to cause severe adverse reactions [234].

Figure 1.9: Mediators responsible for the signs and symptoms of anaphylactic Reactions (from [235])

Class of product	Examples	Biological effects
Enzyme	Tryptase, chymase, cathepsin G, carboxypeptidase	Remodel connective tissue matrix
Toxic mediator	Histamine, heparin	Toxic to parasites Increase vascular permeability Cause smooth muscle contraction
Cytokine	IL-4, IL-13	Stimulate and amplify T_H2 cell response
	IL-3, IL-5, GM-CSF	Promote eosinophil production and activation
	TNF-α (some stored preformed in granules)	Promotes inflammation, stimulates cytokine production by many cell types, activates endothelium
Chemokine	CCL3 (MIP-1α)	Attracts monocytes, macrophages, and neutrophils
Lipid mediator	Leukotrienes C4, D4, E4	Cause smooth muscle contraction Increase vascular permeability Stimulate mucus secretion
	Platelet-activating factor	Attracts leukocytes Amplifies production of lipid mediators Activates neutrophils, eosinophils, and platelets

Figure 12-12 Immunobiology, 6/e. (© Garland Science 2005)

Figure 1.10: Effect of mast-cell degranulation and mediator release on different organs (from [235]



In anaphylactoid reactions the same chemical mediators that cause clinical signs and symptoms of anaphylaxis are also involved, but, the mechanism of mediator release and the immediate systemic reactions are not caused by an IgE-mediated immune response [236] and in most cases are not fully understood.

There are discrepancies in the definition of anaphylaxis and anaphylactoid reactions among different physicians. Some define it as skin involvement only,

and others define a more severe adverse reaction involving cardiovascular, respiratory and gastrointestinal features. It may be difficult in an individual patient to be completely certain of the mechanisms involved, and whether immunological or non-immunological processes are causative.

1-4-4-1: Adverse Reactions to NAC

Since the introduction of the NAC treatment regimen for paracetamol overdose in 1979, there have been reports of anaphylactoid adverse reactions. The first adverse reaction to NAC was reported by Walton et al in 1979 [237]. The reported frequency of such reactions, has varied from 3-9% [238-240] to 48.4% [241] in different population of patients with paracetamol overdose who were treated with NAC.

The full profile of adverse reactions reported includes rash, pruritus, flushing, nausea and vomiting, coughing, dyspnoea, chest pain, bronchospasm, wheezing, angioedema, hypotension, hypertension, tachycardia, ECG changes, and fever [240;242;243]. Some patients seem to be more susceptible to adverse reactions from IV NAC. It has been suggested that asthma is a risk factor for NAC ADRs [244;245] and there has been a report of death in an asthmatic patient [246]. Some studies report that plasma paracetamol concentration is lower in patients with ADRs [239;241;245]. The high incidence of ADRs to IV NAC (50%) in healthy volunteers not receiving paracetamol is further evidence

that paracetamol itself may have some protective effect against ADRs to NAC [231].

The pathophysiological mechanisms involved in ADRs to NAC are not fully understood. In a human study an intra dermal injection of NAC caused a wheal and flare reaction. Some authors suggest that a non-allergic release of histamine which was a direct, dose-dependent effect of NAC to which individuals had variable susceptibility, was the potential mechanism of ADRs [247]. An in vitro study has shown histamine release is induced by NAC [248]. Previous studies on acute allergic reactions and anaphylactic shock in other situations have shown an increase in plasma concentrations of mast cell products (histamine and tryptase) [249-252], endothelial injury parameters (von Willebrand factor [vWf]) and fibrinolytic parameters (tissue plasminogen activator [tPA] [251]. Healthy volunteers given antidotal doses of NAC intravenously who developed adverse reactions had elevated factor VIII and vWf within an hour of starting IV infusion of the therapeutic dose of NAC (400 mg/kg, over 36h, distributed as a 150 mg/kg bolus over 15 min, 50 mg/kg over 4h, and 200 mg/kg over 32h). The authors suggested that NAC induces release of vWf from endothelial cells in subjects who develop adverse effects [231].

Interleukin 6 (IL-6) is known to be secreted by mast cells and basophils and has also been reported to contribute in allergic reactions [253]. As it has a longer half-life (48h) than serum histamine and tryptase, it has been suggested that

IL-6 could have a place as a biomarker in the diagnosis of anaphylactoid reactions [254]. IL-6 also stimulates C-reactive protein (CRP) production and the two correlate with one another in various conditions [255;256] and in acute allergic reactions [257]. Whether these response mechanisms apply in patients with paracetamol overdose is unknown.

There is a need to better understand the risk factors for these reactions since they result in temporary cessation of antidote therapy, cause patient distress, and delay treatment and discharge. If the mechanisms were better understood, effective treatment could potentially be used to prevent the reaction occurring.

1-5: Summary

Paracetamol is the most common analgesic and antipyretic over the counter drug and is well tolerated at therapeutic dose by adults and children. It also has weak anti-inflammatory effect. The mechanism of action of paracetamol includes inhibition of cyclo-oxygenase and prostaglandin synthesis; however, the precise mechanism of action is still unclear. In overdose it causes toxicity and this is a major public health problem in the UK. Forty percent of all overdose presentation to the hospital involve paracetamol, and it is the main cause of acute liver failure, resulting in several hundred liver unit admissions and substantial deaths each year in the UK. The liver is the main target organ affected in paracetamol overdose.

The kidney controls electrolyte and acid-base homeostasis, and maintains the content of extracellular fluid. Nephrotoxicity may be caused by a wide variety of drugs and substances which are readily available in routine life, and the workplace. Nephrotoxic agents can cause different types of renal failure according to the site of action. Acute tubular necrosis is the most common type of acure renal failure caused by drugs.

Cyclo-oxygenase I and II are both expressed in the kidney and synthesise prostaglandin in the kidney. Prostaglandins are essential for the maintenance of renal perfusion. If there is reduction in actual, or effective, circulating volume, they influence water and electrolyte homeostasis.

Some drugs including NSAIDs have inhibitory effects of cyclo-oxygenase resulting in renal failure, in particular in patients with risk factors. Such an acute renal impairment is mediated through inhibition of renal prostaglandin synthesis, resulting in vasoconstriction and renal hypoperfusion. The kidney is also involved in paracetamol toxicity, even in the absence of liver injury. The mechanisms of nephrotoxicity are not fully understood; however, a specific renal effect of paracetamol possibly due to inhibitory effect on cylo-oxygenase and prostaglandin synthesis has been suggested. Electrolytes abnormalities, in particular potassium abnormalities may occur following renal dysfunction, including drug-induced acute renal failure. Early diagnosis, recognition of associated risk factors, prevention and follow up of different kidney diseases, in particular drug-induced nephropathy, is an important issue in the practice of medicine. Whether the toxic effects of paracetamol on the kidney are due to similar mechanisms to NSAIDs remains unclear. The relationship between renal and hepatic damage in paracetamol overdose is also uncertain.

NAC is a treatment of choice in paracetamol poisoning. Some patients develop adverse reactions following intravenous infusion of NAC. The mechanisms of the reactions are not clear. A possibility of histamine related mechanism for the adverse reactions has been suggested.

1-6: The focus of the thesis

This thesis composes of studies in which different aspects of paracetamol poisoning have been explored. The main focus of the first three studies is on the nephrotoxic aspects of paracetamol overdose. Initially the effect of paracetamol overdose on plasma electrolytes was examined, and then the mechanisms involved in plasma electrolyte change were identified in a prospective intensive study, based on data collected from timed blood and urine collections at intervals after overdose. In the third study the frequency of renal injury on patients with severe paracetamol overdose admitted to a liver unit was assessed retrospectively, and risk factors for renal injury and poor outcome assessed.

The last three studies focus on the treatment of paracetamol poisoning. In the fourth study the frequency of liver failure in patients who had paracetamol concentrations under the current “treatment line” and who, therefore were not treated with NAC, was explored. In the fifth study the risk factors for adverse reactions to IV NAC in a cohort of patients requiring therapy were examined. Finally, a small intensive study investigating the mechanisms of adverse reactions to NAC was conducted in patients with paracetamol overdose who required antidote treatment.

Chapter II: Effect of Single Paracetamol Overdose on Renal Function and Plasma and Urine Electrolytes

2-1: Introduction

A number of mechanisms have been proposed to explain the analgesic and antipyretic effects of paracetamol. Paracetamol can inhibit cyclo-oxygenase (COX) but, in contrast to non-sterodial anti-inflammatory drugs (NSAIDs), does not have anti-inflammatory effect due to lack of peripheral inhibition of prostaglandin (PG) synthesis [258]. Selective inhibition of COX-III by paracetamol, a variant of COX-I resulting in central inhibition of PG synthesis was proposed by Chandrasekharan [11]. However, there is also some in vivo evidence showing that, in addition to its CNS inhibitory effects on COX-III, paracetamol can, in fact, inhibit COX-II systemically in a manner similar to the selective COX-II inhibitors [8;10].

Renal PG production is mediated primarily by COX, and plays a major role in compensatory renal hemodynamics. NSAIDs have a variety of effects on the kidney. Severe adverse renal effects may be in part due to vasoconstriction, consequent upon inhibition of renal PG-mediated vasodilatation. This decreases renal blood flow, and results in a reduction in glomerular filtration rate [259]. NSAID-induced acute renal failure depends on the drug, dose, duration of pharmacologic effect, and the health of patient. Generally, individuals who are well hydrated and have normal renal function are unlikely to develop acute renal failure [260].

Paracetamol in overdose can cause renal failure. The actual mechanism of paracetamol-induced nephrotoxicity in man is not fully understood. There is a possibility that at high doses paracetamol-induced nephrotoxicity may be due to local haemodynamic changes, perhaps through COX inhibitory effects in the kidney similar to classical NSAIDs. It has previously been shown, in a study on Wistar rats, that single doses of paracetamol caused a significant reduction in glomerular filtration rate (GFR) and renal blood flow in a dose dependent manner [194]. This altered tubular function, mainly in the distal tubules, observed as a change in renal concentrating ability. The maximum changes were observed at 16 h post-ingestion, and after 24 h renal function was restored. The authors suggest that the early stage of paracetamol-induced nephrotoxicity might be due to vasoconstriction. Other work has shown phosphaturia after paracetamol overdose, possibly due to tubular effects of paracetamol [198;199]. However, studies on therapeutic doses of paracetamol have found no effect on plasma electrolytes in man [193;261].

It has previously been shown that in overdose NSAIDs, such as ibuprofen, increase fractional excretion of potassium and cause sodium retention [262] an effect that might to be due to renal vasoconstriction and consequent activation of the renin-angiotensin-aldosterone system.

It was hypothesized that paracetamol in overdose might cause similar tubular effects to NSAIDs via inhibition of PG synthesis, secondary vasoconstriction and

activation of renin-angiotensin-aldosterone system which would be identified by change in electrolyte handling and urine electrolytes.

In this chapter two separate studies, retrospective and prospective, conducted on patients with paracetamol overdose will be discussed. In the retrospective study the effect of paracetamol overdose on plasma electrolytes and in the prospective study its effect on plasma and urine electrolytes were investigated.

2-2: Retrospective study

2-2-1: Methods

A retrospective cross-sectional study was conducted on patients, male and female, age 16-60 year-old, presenting with single acute paracetamol overdose within 6 hours (h) post-ingestion and admitted to the toxicology ward of Royal Infirmary of Edinburgh from January 2002 to May 2006. Information regarding name of tablets taken, time of ingestion, time of presentation to the hospital, acetylcysteine (NAC) treatment, other treatment, change in blood pressure and past medical history was collected from patient notes. Laboratory test results (plasma paracetamol, plasma sodium [Na] and potassium [K] and plasma creatinine [Cr]), time and date of sample collection were obtained from the hospital laboratory computer system.

Case notes of patients presenting within 6 h of a stated ingestion of single paracetamol were reviewed. Records of patients who had at least two blood tests at 4-6 and 12-24 h post ingestion were extracted and examined to exclude later presentations to the hospital (after 4-6 h post-ingestion), mixed overdose, staggered overdose (taking tablet over period of longer than 2 h), pregnancy, and chronic underlying diseases, including history of kidney disease, liver disease, heart disease, hypertension and diabetes. Patients who had co-ingested benzodiazepines and/or ethanol with paracetamol were included, as these compounds are not thought to be nephrotoxic. Patients who were on regular prescribed potentially nephrotoxic drugs according to the British National Formulary [31] and cases with missing information, were excluded from the study.

The biochemistry results of blood samples on admission (within 4-6 h post-ingestion) and 12-24 h post-ingestion (plasma paracetamol, Cr, Na, K, and bicarbonate [HCO_3]) were extracted from the hospital computerised laboratory results system. The relationships between plasma paracetamol concentration at admission, “4 h”, and subsequent changes in plasma electrolytes seen during the period of admission were examined.

Patients were divided into three subgroups according to the plasma paracetamol at 4 h post-ingestion for illustrative purposes: group 1: patients with plasma paracetamol <100 mg/l (low risk treatment threshold), group 2: patients

with plasma paracetamol 100-199 mg/l (high risk treatment threshold), and group 3 with plasma paracetamol ≥200 mg/l (normal treatment threshold). In the UK NAC is differentially given to patients with specified “risk factors” [31] in addition to a high plasma paracetamol.

2-2-2: Statistical analysis

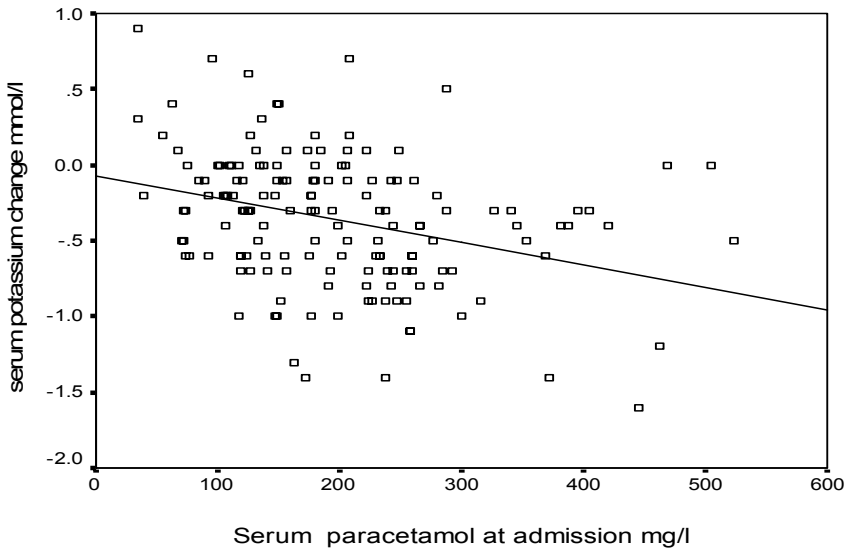
SPSS version 11.5 was used for statistical analysis. The data was normally distributed; and therefore parametric tests were used for statistical analysis. Demographic data and two group comparisons were compared using unpaired independent student t-test and Mann-Whitney U test as appropriate. Multiple comparisons were made by one-way analysis of variance (ANOVA) with post-hoc Bonferroni test and Kruskal-Wallis H test as appropriate. Correlation between variables was made by Pearson correlation test. Data are reported as mean ± standard error of the mean (sem).

2-2-3: Results

155 patients with paracetamol overdose met the inclusion criteria. 38% were male (n=59) and 62% (n=96) female. The patients had mean age of 32.3 ± 2.6 years. There was a significant correlation (R^2=0.10, p<0.0001, n=155, Figure 2.1) between admission plasma paracetamol (mg/l) and fall in plasma potassium (mmol/l) between the admission and second blood sample. The

mean time between blood samples was 22.0 ± 0.37 h. The negative dose-dependent relationship between plasma paracetamol at 4 h and fall in plasma K remained when only patients receiving NAC were considered (r= -0.25, p<0.01, n=139, reduction in plasma K from 3.86 ± 0.04 to 3.46 ± 0.03 mmol/l, n=139).

Figure 2.1: Relationship between plasma potassium change (mmol/l) between admission (4 h) and follow-up plasma K and plasma paracetamol (mg/l) at 4 h post ingestion in the retrospective study. Mean time difference between two samples was 22.0 ± 0.37 h. n= 155, r=0. -0.32, p<0.0001.

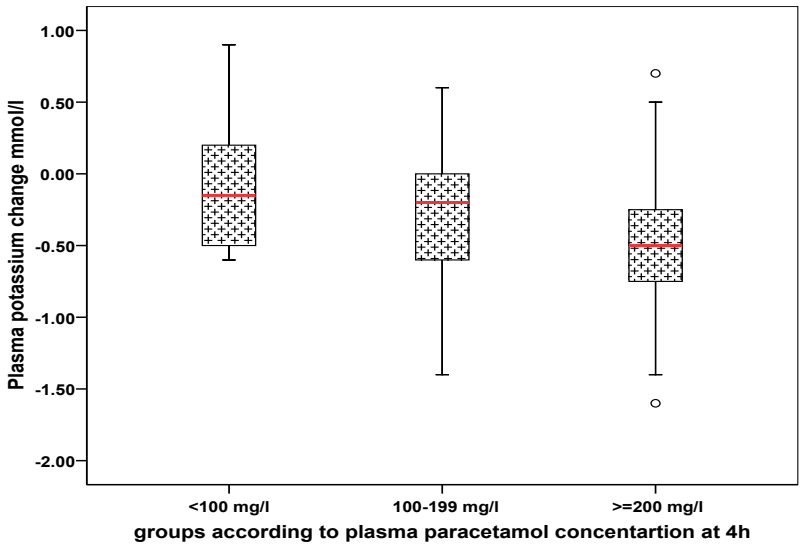


When patients were grouped according to admission paracetamol level, the mean plasma paracetamol was 69.9 ± 4.4 mg/l in group 1 (<100 mg/l, n=18), 146.0 ± 3.4 mg/l in group 2 (100-199 mg/l, n=69), and 283.3 ± 9.5 mg/l in group 3 (≥200 mg/l, n=68). The mean reduction in plasma potassium in the group with

highest paracetamol concentration was -0.5 ± 0.05 mmol/l. There was a significant difference in change in plasma potassium between groups with low (-0.08 ± 0.10 mmol/l) and high (-0.50 ± 0.05 mmol/l), ($p<0.01$), and medium (-0.31 ± 0.05 mmol/l) and high paracetamol concentration at admission, ($p<0.05$) (Figure 2.2).

Figure 2.2: Change in plasma potassium (mmol/l) in the groups according to the plasma paracetamol concentration at 4h in the retrospective study.

Data shown by risk category (plasma paracetamol <100 mg/l (low, 69.9 ± 4.4, n=18), 100-199 mg/l (medium, 146.0 ± 3.4, n=69), and ≥ 200 mg/l (high, 283.3 ± 9.5, n=68), in box and whisker format (Median, interquartile box). There was a significant difference in the change in plasma potassium between groups with low (-0.08 ± 0.10 mmol/l) and high (-0.50 ± 0.05 mmol/l), ($p<0.01$), and medium (-0.31 ± 0.05 mmol/l) and high paracetamol concentration at admission, ($p<0.05$) Circle shows outliers which are cases with values between 1.5 and 3 box lengths from the upper and lower edge of the box. The box length is the interquartile range.



If only patients receiving NAC were considered, the negative dose-dependent relationship between plasma paracetamol at 4 h and plasma potassium change remained (R2: 0.06, $p<0.01$, n=139, and plasma potassium fell from 3.86 ± 0.04 to 3.46 ± 0.03 mmo/l) (see table 2.1 for the number of patients treated with NAC and plasma paracetamol concentrations in each group).

Table 2.1: Numbers of subjects in each group according to the plasma paracetamol level at 4 h and NAC treatment in the retrospective study. n=155.

Groups according to plasma paracetamol level	**n**		**Plasma paracetamol (mg/l)**	
	With NAC	**Without NAC**	**With NAC**	**Without NAC**
Group 1	10	8	56.29 ± 8.29	78.00 ± 3.29
Group 2	61	8	145.59 ± 3.54	149.00 ± 11.60
Group 3	68	0	283.31 ± 9.46	-

Blood pressure did not change significantly in either paracetamol or control group. Vomiting did not affect change in plasma K significantly (plasma K in the group with vomiting: -0.38 ± 0.05 mmol/l, n=94, vs. group without vomiting: -0.34 ± 0.06 mmol/l, n=61). There was neither correlation between plasma paracetamol and changes in plasma HCO3 nor between change in plasma K and plasma HCO3. There was also no correlation between changes in plasma Na or plasma Cr with plasma paracetamol.

2-3: Prospective study

2-3-1: Method

A prospective cohort study was conducted on patients, presenting with a single paracetamol overdose and admitted to the toxicology ward of the Royal Infirmary of Edinburgh from July 2004 to April 2006. Subjects who were recruited to the prospective study were not included in the retrospective study. Inclusion criteria were patients, male and female, aged 16y and over, with single paracetamol overdose with or without alcohol co-ingestion, presenting to hospital within 6 h post-ingestion. Exclusion criteria included later presentations to hospital (>6 h post-ingestion); mixed overdose; staggered overdose; pregnancy (relied on patient history and physical exam, not specifically verified by pregnancy test); underlying chronic disease, including history of kidney disease, liver disease, heart disease, hypertension and diabetes, patients who were on regular prescribed potentially nephrotoxic drugs; patients who were not conscious at admission, and those who had learning difficulty. Patients who withdrew from the study or were not able to give blood and urine samples within 6 h and/or at least one blood and urine samples at either 12 h or 24 h post-ingestion were also excluded. As a control group patients with single overdose of fluoxetine or paroxetine according to the patient's history were recruited as an example of SSRI ingestion (selective serotonin reuptake inhibitors). Inclusion and exclusion criteria for the control group were the same as paracetamol group.

The study was approved by the local Ethics Committee, and informed consent was obtained on admission (see appendix 2.1, 2.2, 2.3 and 2.4). Subjects were interviewed at admission to hospital, and information regarding name of tablets taken, alcohol ingestion, time of ingestion, time of presentation to the hospital, vomiting, medical history and drug history was obtained (see appendix 2.5, 2.6 and 2.7).

At 4 to 6 h after ingestion, a paired blood sample (5ml) for measurement of plasma paracetamol and salicylates, plasma Na, K, HCO_3, Mg, PO_4, Cr, osmolality) and a urine sample (10ml, in universal container, for measurement of urine Na, K, Mg, PO_4, Cr, osmolality) were collected. When subjects were not able to give a urine sample at the time of blood collection a urine sample was taken within two h of blood collection. Further paired blood and urine samples were taken at 12 h and at 24 h post ingestion. Blood and urine samples were sent to the Biochemistry laboratory, Royal Infirmary of Edinburgh, within 30 minutes of collection for analysis. Not all patients complied fully with urine collection protocols, and data reported relates to subjects completing a particular study component, however, all subjects included in the analysis had paired blood and urine samples taken within 6 h and at least another paired blood and urine samples at either 12 h or 24 h post-ingestion.

Fractional excretion (Fe) in percent was calculated for Na, K, PO_4 and Mg from [urinary/plasma concentration of electrolyte] x [plasma/urinary concentration of Cr]*100. Trans tubular potassium gradient (TTKG) was calculated from [urinary/plasma K] x [plasma/urine osmolality]. Renal threshold of phosphate concentration (TmP/GFR: the ratio of the maximum rate of renal tubular phosphate reabsorption to the glomerular filtration rate [GFR]) was calculated based on an established nomogram [103].

The relationships between plasma paracetamol at admission “4 h level” with changes in plasma and urine electrolytes at 12 h and 24h post-ingestion were examined. The predictive value of urinary electrolytes in early detection of creatinine rise was also studied. We grouped patients into 3 subgroups according to the plasma paracetamol at 4 h post-ingestion for illustrative purposes: group 1: patients with plasma paracetamol less <100mg/l, group 2: patients with plasma paracetamol 100-199 mg/l, and group 3 with plasma paracetamol 200 mg/l and above.

Blood pressure and pulse rate was recorded at admission and at the time of blood and urine collection. The observational chart documented routinely by nursing staff was also reviewed to exclude haemodynamic compromise as a cause of renal dysfunction. Systolic blood pressure less than 90 mmHg or diastolic blood pressure less than 50 mmHg was considered as hypotension.

2-3-2: Laboratory techniques

Plasma paracetamol was measured by an enzymic method using aryl acyl amidase to produce p-aminophenol which reacts with tetrahyroquinoline and was measured at 670 nm on a Vitros 250 analyser. Plasma and urine Na and K were measured by indirect reading in selective electrolytes on Olympus AU 2700 analyser. Plasma and urine Mg were measured by complexing to Xylidyl blue in a basic solution and measured at 520 nm on an Olympus AU 2700 analyser. Plasma and urine inorganic PO_4 were measured by complexing to molybdate and measured at 340 nm on an Olympus AU 2700 analyser. Plasma HCO_3 was measured by enzymic method: phosphoenolpyruvate carboxylase linked to malate dehydrogenase was measured at 340 nm on an Olympus AU 2700 analyser. Plasma and urine osmolality were measured using freezing point depression. Plasma and urine Cr were measured using kinetic colour test (Jaffe method) on Olympus AU 2700 analyser (all laboratory tests were performed by laboratory technicians in the Royal Infirmary of Edinburgh clinical laboratories).

2-3-3: Statistical analysis

SPSS version 11.5 was used for statistical analysis. Data was tested for normality. As data in each group was not normally distributed, non-parametric tests were used for comparison analysis**.** Mann-Whitney U test was used for two-group comparison. Multiple comparisons between groups were made using Kruskal-Wallis H test. Correlation between variables was made using Pearson

and Spearman correlation test as appropriate. Data are reported as mean ± standard error of the mean (sem).

2-3-4: Results

41 cases of paracetamol overdose, 16 male and 25 female, and 18 cases of SSRI overdose (16 fluoxetine and 2 paroxetine), 7 male and 11 female, completed the study. In both groups 39% were male and 61% female. There was no significance difference in either group in respect of age and gender. In the paracetamol group mean age was 30.0 ± 1.9 years and in the control SSRI group 28.6 ± 2.6 years (Table 2.2). In the paracetamol group, a kaliuresis occurred at 12 h. FeK and TTKG at 12 h post-ingestion were significantly correlated with plasma paracetamol at admission ($r=0.55$, $n=34$, $p<0.01$ and $r=0.46$, $n=34$, $p<0.01$, respectively).

FeK and TTKG at 12 h were significantly different between groups with low and medium ($p<0.01$ and $p<0.05$, respectively), and between low and high plasma paracetamol at admission ($p<0.01$ in both cases, Figures 2.3 and 2.4). This change was no longer evident at 24 h.

Table 2.2: Demographic characteristics of subjects and study variables in paracetamol and SSRI groups. NS: not significant.

Variable	Groups	number	mean± sem	Significance level
Gender (F/M)	Paracetamol	25/16		NS
	SSRI	11/7		
Age (Y)	Paracetamol	41	30.04 ± 1.89	NS
	SSRI	18	28.59 ± 2.63	
Change in plasma K at 4-12 h (mmol/l)	Paracetamol	37	-0.28 ± 0.05	p<0.01
	SSRI	18	-0.07± 0.08	
Change in plasma K at 4-24 h (mmol/l)	Paracetamol	31	-0.23± 0.09	NS
	SSRI	10	-0.05 ± 0.18	
FeK at 4 h (%)	Paracetamol	41	16.06 ± 1.46	p<0.01
	SSRI	18	8.74 ± 1.43	
FeK at 12 h (%)	Paracetamol	34	16.47 ± 1.70	p=0.05
	SSRI	16	11.38 ± 1.80	
FeK at 24 h (%)	Paracetamol	31	7.35 ± 1.2	NS
	SSRI	9	7.20 ± 1.48	
Plasma osmolality at 4 h (mosmol/kg)	Paracetamol	40	300.08 ± 3.55	NS
	SSRI	17	302.71± 3.91	
Plasma osmolality at 12 h (mosmol/kg)	Paracetamol	37	290.24 ± 2.06	NS
	SSRI	18	294.83 ± 2.76	
Plasma osmolality at 24 h (mosmol/kg)	Paracetamol	32	287.69 ± 1.29	NS
	SSRI	10	288.90 ± 1.62	
Urine osmolality at 4 h (mmol/kg)	Paracetamol	41	600.12 ± 49.09	NS
	SSRI	18	581.11 ± 65.81	
Urine osmolality at 12 h (mmol/kg)	Paracetamol	34	659.94 ± 48.55	NS
	SSRI	17	777.53 ± 68.99	
Urine osmolality at 24 h (mmol/kg)	Paracetamol	31	462.26 ± 42.89	P<0.01
	SSRI	9	905.22 ± 42.80	
Change in plasma creatinine at 12 h (µmol/l)	Paracetamol	32	-0.94 ± 1.35	NS
	SSRI	9	2.22 ±1.64	
Change in plasma creatinine at 24 h (µmol/l)	Paracetamol	37	-1.68 ± 0.83	NS
	SSRI	18	1.39 ± 1.42	

Figure 2.3: Time course of FeK changes according to plasma paracetamol at 4 h in the prospective study.

Data shown by risk category (plasma paracetamol <100 mg/l (low, 61.3 ± 6.5), 100-199 mg/l (medium, 141 ±. 5.4), and >=200 mg/l (high, 286.6 ± 30.0), in box and whisker format (Median, interquartile box). FeK at 12 h was significantly different between groups with low and medium ($p<0.01$) and low and high plasma paracetamol ($p<0.01$). Para: plasma paracetamol (mg/l). (Circle shows outliers which are cases with values between 1.5 and 3 box lengths from the upper and lower edge of the box. The box length is the interquartile range. Asterisk shows extremes which are cases with values more than 3 box length from the upper and lower edge of the box.)

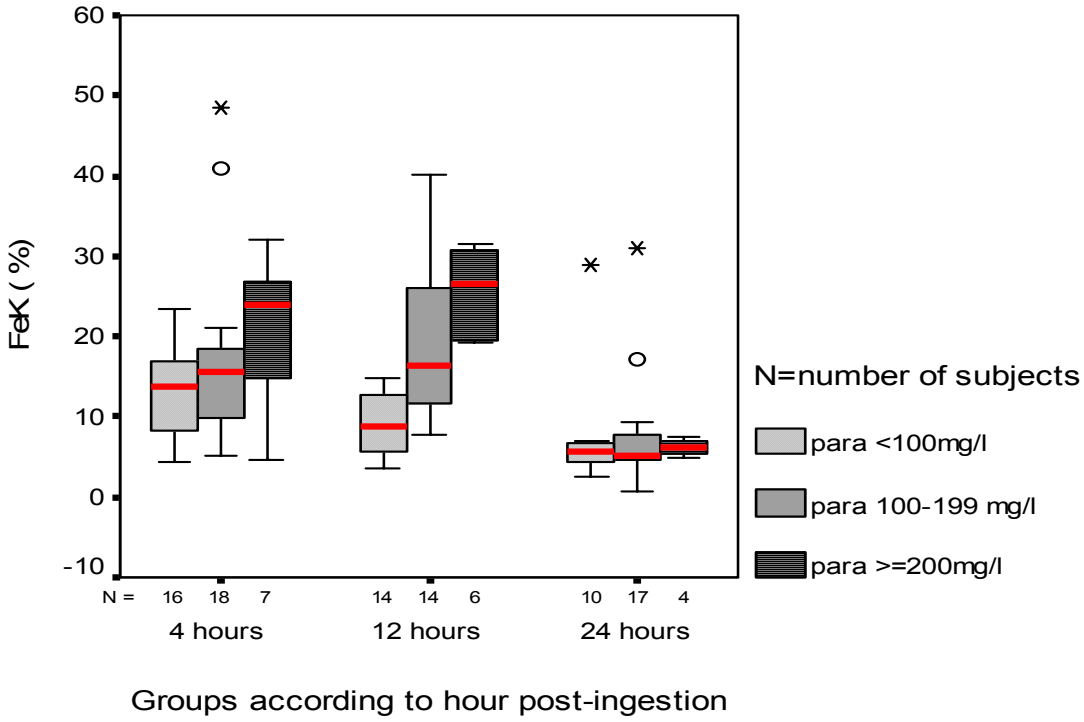
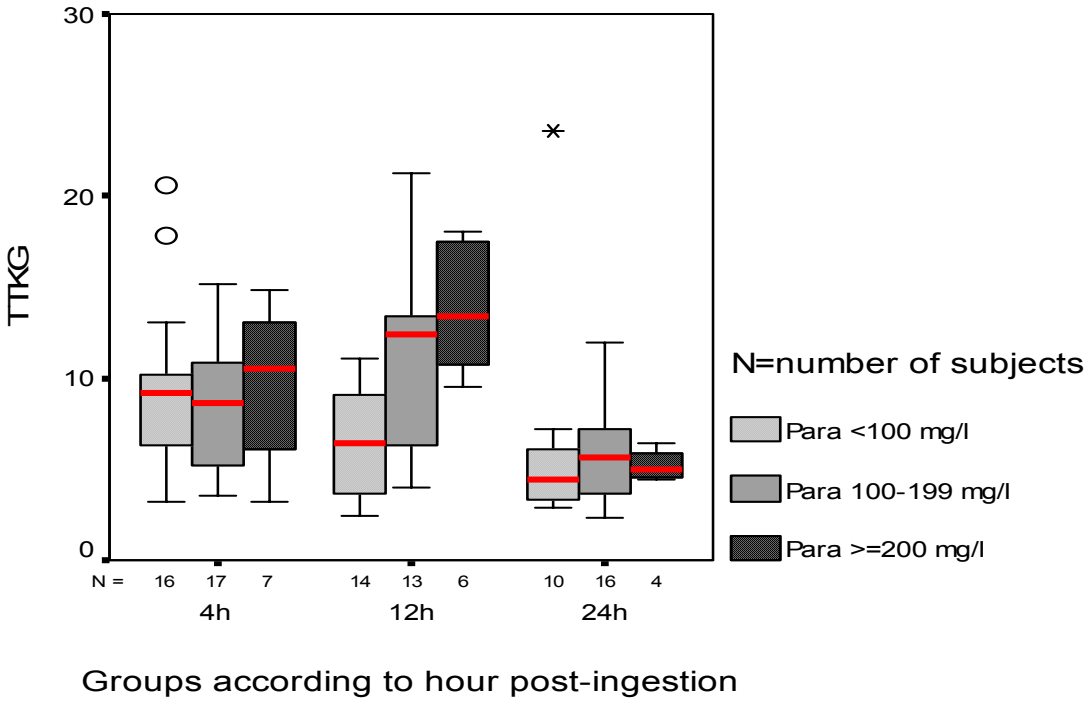


Figure 2.4: Time course of TTKG changes according to plasma paracetamol at 4 h in the prospective study.

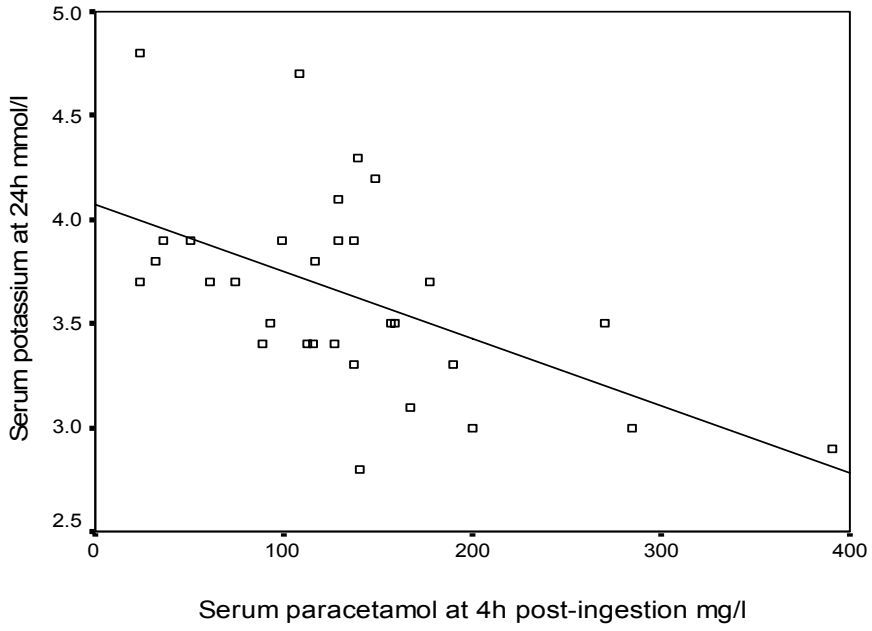
Data shown by risk category (plasma paracetamol <100 mg/l (low, 61.3 ± 6.5), 100-199 mg/l (medium, 141 ±. 5.4), and ≥ 200 mg/l (high, 286.6 ± 30.0), in box and whisker format (Median, interquartile box). TTKG at 12 h was significantly different between groups with low and medium ($p<0.05$) and low and high plasma paracetamol ($p<0.01$). Para: plasma paracetamol (mg/l). (Circle shows outliers which are cases with values between 1.5 and 3 box length from the upper and lower edge of the box. The box length is the interquartile range. Asterisk shows extremes which are cases with values more than 3 box length from the upper and lower edge of the box.)



At 24 h, plasma potassium was in a negative dose-dependent relationship with plasma paracetamol ($r= -0.54$, $p<0.01$, $n= 31$, Figure 2.5). No relationship was seen in the control SSRI group between stated dose of ingested drug and plasma K or FeK. The mean plasma K change was significantly different

between paracetamol group and control group at 12h (-0.28 ± 0.05 mmol/l vs. -0.07 ± 0.08 mmol/l) (Table 2.1).

Figure 2.5: Relationship between plasma potassium (mmol/l) at 24 h post-ingestion and plasma paracetamol (mg/l) at 4 h in the prospective study, r= -0.54, n=31, p<0.01.



No effect on plasma or urinary electrolytes was seen in the SSRI group. There was no relationship between stated ingested doses of SSRI and plasma or urine electrolytes. Plasma and urine electrolytes did not significantly change at different time points after ingestion (Table 2.3).

Table 2.3: Fraction excretion of electrolytes (Na, Mg, PO4) at different time points after ingestion in the control group (SSRI). Nonparametric test (Kruskal-Wallis), (NS: not significant). N=number

Variables	4 h		12 h		24 h		Sig.
	Mean±sem	n	Mean±sem	n	Mean±sem	n	
FeK (%)	8.78±1.43	18	11.38±1.8	16	7.18±1.48	9	NS
Plasma K (mmol/l)	4.00±0.07	18	3.93±0.06	18	3.94±0.11	10	NS
FeNa (%)	0.57±0.08	18	0.46±0.06	17	0.41±0.07	9	NS
Plasma Na (mmol/l)	140.28±0.44	18	140.72±0.39	18	139.5±0.82	10	NS
FeMg (%)	3.09±0.37	18	1.89±0.24	17	2.7±0.47	9	p<0.05
Plasma Mg (mmol/l)	0.84±0.02	18	0.83±0.02	18	0.87±0.02	10	NS
FePO4 (%)	9.38±2.20	18	18.78±2.10	15	14.22±3.23	9	NS
Plasma PO_4 (mmol/l)	1.09±0.05	18	1.17±0.04	16	0.91±0.12	10	NS

There was consequently a significant difference between paracetamol and SSRI group in FeK at 4 h and plasma K change at 12h ($p<0.01$). The difference in FeK at 12 h between 2 groups was in borderline significance difference ($p=0.05$). The difference in FeK and plasma K change had disappeared by 24 h (Table 2.1).

In both groups (paracetamol and SSRI) the ratio of urinary osmolality to plasma osmolality (U/P) was high at 4 h (U/P osmolality at 4 h: 2 in paracetamol group and 1.9 in SSRI group) and 12 h (U/P osmolality at 12 h: 2.2 in paracetamol

group and 2.6 at SSRI group), but, there was no significant difference between groups. In the paracetamol group U/P osmolality was restored after 24 h (U/P osmolality at 24 h: 2); however, this continued increasing in the SSRI group (U/P osmolality at 24 h: 3.1) and that was significantly higher than that of paracetamol group ($p<0.0001$) (Table 2.2). There was no significant difference in plasma and urinary excretion of K and PO_4 at 4 h, 12 h and 24 h in the paracetamol group with (n=31) and without (n=10) co-ingestion of alcohol.

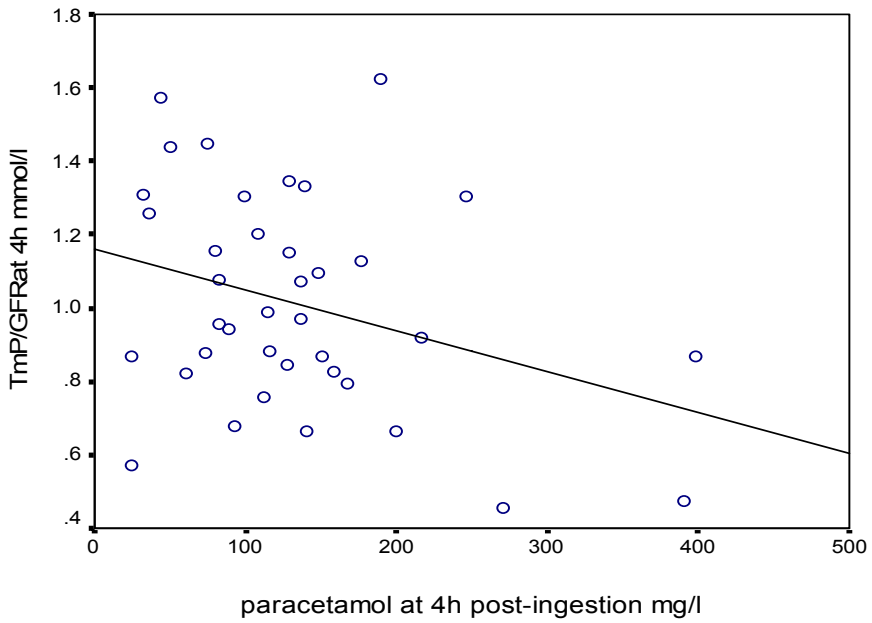
Plasma paracetamol was in a negative dose dependent correlation with plasma PO_4 (mmol/l) ($r=-0.44$, $n=39$, $p<0.01$) and renal threshold phosphate concentration (TmP/GFR, mmol/ll) ($r=0-0.33$, $n=38$, $p<0.05$) at 4 h (Figure 2.6). Plasma PO_4 decreased at 12 h and 24 h but $FePO_4$ increased at 12 h and consequently decreased at 24 h (Table 2.4). In SSRI group plasma PO_4 and $FePO_4$ did not change significantly at 12 h and 24 h (Table 2.3).

Plasma and urinary Mg did not change in the paracetamol group (Table 2.4), however, in the SSRI group there was a reduction in FeMg at 12 h. FeNa reduced in paracetamol group without any significant change in plasma Na. No effect on plasma Na or FeNa was seen in the SSRI group (Table 2.3).

Table 2.4: Plasma concentrations and fractional excretion of electrolytes (K, Na, Mg, PO4) at different time points after ingestion of paracetamol. NS: not significant, n=number.

Variables	4 h		12 h		24 h		Sig. level
	Mean ±sem	n	Mean ±sem	n	Mean ±sem	n	
FeK (%)	16.07±1.47	41	16.47±1.70	34	7.36±1.20	31	P<0.01
Plasma K (mmol/l)	3.90±0.05	41	3.62±0.06	37	3.65±0.09	31	P<0.01
FeNa (%)	0.64±0.07	41	0.56±0.05	34	0.40±0.05	31	P<0.05
Plasma Na (mmol/l)	139.02±0.4	41	138.89±0.48	37	138.81±0.54	31	NS
FeMg (%)	2.36±0.26	40	2.15±0.24	32	2.52±0.26	9	NS
Plasma Mg (mmol/l)	0.81±0.02	40	0.74±0.05	35	0.84±0.02	30	NS
FePO4 (%)	15.28±1.8	38	19.12±1.17	30	12.51±1.51	29	P<0.05
Plasma PO4 (mmol/l)	1.18±0.04	39	1.15±1.0.46	36	0.90±0.40	32	P<0.01

Figure 2.6: Relationship between renal threshold phosphate concentration (TmP/GFR) (mmol/l) and plasma paracetamol at 4 h in the prospective study, n= 38, r= -0.33, p<0.05



Vomiting did not affect plasma potassium significantly. Additionally, there was no correlation between changes in plasma HCO_3 and in plasma K, or between plasma HCO_3 and plasma paracetamol. There was no change in plasma Cr. Only 3 cases in the paracetamol group developed features of liver injury (rise in ALT) at 24 h. Plasma Cr in these three cases was in the normal range. Blood pressure did not change significantly in either paracetamol or control groups.

2-4: Discussion

Understanding the processes by which paracetamol affects the kidney in overdose is key to any prediction of renal toxicity, and evaluation of potential antidotal therapy. Identification of patients at risk of renal failure would enable them to be targeted for special monitoring and intervention. Most cases of paracetamol intoxication seen in the UK are discharged within a 24 h time frame, during which hepatic toxicity can be predicted, and appropriate treatment continued, or commenced. This is not the case in renal toxicity, which develops later. The true extent of renal toxicity is unknown, since only the most severe forms re-present as acute renal failure. According to the clinical experience of patients presenting to the Toxicology unit of Royal Infirmary of Edinburgh one or two out of 1000 cases with paracetamol overdose may develop renal failure without significant liver involvement (rise in ALT).

The main finding of the retrospective study was the dose-dependent relationship between 4 h plasma paracetamol and fall in plasma K. The prospective study also demonstrated a relationship between 4 h plasma paracetamol and 24 h plasma K and additionally showed an increase in FeK and TTKG at 12 h post-ingestion, again in dose-dependent relationship with plasma paracetamol that had normalised by 24 h. These changes in K were not seen in the SSRI control group. Because no patients studied developed a significant rise in Cr, it is not possible to state these findings are relevant to the development of nephrotoxicity. However, the results of the retrospective and prospective studies were consistent with the results of a previous pilot study on ibuprofen overdose, a classical NSAID. This also showed a dose-dependent relationship between dose of ibuprofen ingested and FeK [262].

The most common causes of hypokalemia from renal K loss are due to either medication, endogenous hormone production or in rare cases, intrinsic renal defects [94]. The dose-dependent relationship between plasma paracetamol and FeK at 12 h post-ingestion implicates renal loss of K to explain the hypokalaemia observed in paracetamol overdose. However, there were some confounding factors which might affect change in plasma K.

Firstly hydration may have had an effect as the group of patients with high paracetamol received NAC in 5% plasma dextrose (total volume of 1700 ml). However, there was no significant change in plasma Na relating to NAC

treatment in either study, or change in plasma osmolality in the prospective study, indicating that it is very unlikely that hypokalemia was a result of dilution.

Secondly, since only cases with a particular risk or high plasma paracetamol received NAC infused in 5% dextrose, this may have altered plasma K levels through endogenous insulin production induced by the 5% dextrose, resulting in movement of K into the intra-cellular compartment. NAC might also have affected tubular K handling directly. To determine the effect of NAC and 5% dextrose on plasma K and FeK, the ideal would be to compare these measurements in two groups with the same plasma paracetamol who did and did not receive NAC treatment. However, due to unequal distribution of subjects in each group, it was not possible to define such groups for comparison (Table 2.4). To address this, in the retrospective study the relationship between plasma paracetamol at 4 h and plasma K change over 20 h in the NAC treated group alone was examined. The significant relationship seen in all subjects persisted in this subset. While this does not rule out an effect of NAC, it does suggest that plasma paracetamol itself is a factor in plasma K change. Further studies investigating the actual effect of NAC in 5% dextrose on renal function and electrolyte handling and plasma K in healthy volunteers are required to define this further.

Thirdly, vomiting is known to cause hypokalemia as a consequence of metabolic alkalosis. However, in neither retrospective nor prospective studies could an

effect of vomiting be found. In addition, change in plasma K and FeK did not show association with change in plasma HCO_3, which would be expected if vomiting changed K by causing alkalosis.

As a small number of patients had ingested alcohol before or with drug (n=10) in the prospective study, there might be a potential effect of alcohol. An experimental study on rats investigating the acute effect of ethanol on renal electrolyte transport showed diuresis, an increase in FeNa and no change in FeK within an hour after acute ingestion of ethanol [263]. Another animal experiment studying the acute effect of ethanol on renal hemodynamics and monovalent ion excretion over a longer period showed an increase in excretion of sodium at 2 h, 10 h, 18 h and 26 h post-ingestion and a biphasic change in potassium excretion [264] while potassium excretion decreased at 2 h and started increasing at 10 h, 18 h and 26 h. The maximal change was seen at 18 h. In the current study, plasma alcohol was not measured, however, changes in plasma and urine electrolytes in the groups with and without alcohol ingestion was compared. The results of the current study did not show a significant difference in plasma Na, K, Mg, PO_4, FeNa, FeK, FeMg and $FePO_4$ between these groups, suggesting that alcohol is unlikely to be a major contributor to the changes in plasma and urine electrolytes observed. A further study in a larger group of subjects with measurement of plasma alcohol could give a better understanding of dose and time dependent effect of alcohol on electrolyte handling in paracetamol overdose.

Finally, paracetamol in aqueous solution has a pH of 6.24 [261]. While the buffering capacity of plasma is large, it is possible that a high plasma paracetamol is associated with a mild acidosis that resolves as the paracetamol falls. This would result in K shifts between the plasma and the intracellular compartment. However, there was no correlation between plasma HCO_3 and paracetamol. Additionally, acidosis would be associated with plasma K egress from the intracellular compartment, increasing plasma K, the converse of the result observed in this study.

In a study on Wistar rats [194], the effect of different single doses of paracetamol on renal function and electrolytes handling was examined. GFR and renal plasma flow significantly decreased in a dose-dependent manner. Time course of changes in electrolyte excretion in the group given toxic dose of paracetamol (1000 mg/kg) showed an increase in FeK and no change in FeNa at 1 h, 6 h, and 16 h. The maximal change in FeK and renal perfusion was at 16 h post-ingestion and was restored at 24 h. The authors suggested that early stages of paracetamol nephrotoxicity are due to renal haemodynamic changes. In the current study, renal blood flow was not measured, nor did plasma Cr change significantly, though this is a relatively insensitive marker of small changes in GFR. The major changes seen in this study were in K with the maximum derangement in FeK occurring after 12 h and restored after 24 h which was consistent with the results of animal study.

Aldosterone is the most important hormone regulating total body K homeostasis, causing hypokalemia by stimulating K uptake into cells and increasing renal K excretion [94]. Aldosterone secretion is increased by renal hypoperfusion via activation of the renin-angiotensin-aldosterone axis. The results of the current study could therefore be consistent with the early effects of paracetamol toxicity being due to renal haemodynamic change consequent upon activation of the renin-angiotensin-aldosterone axis, seen here as increasing K excretion and Na retention.

In the SSRI group an increase in urine osmolality at 4 h, 12 h and 24 h supports the results of previous studies [265-267], in which hyponatremia secondary to SSRI-induced syndrome of inappropriate anti diuretic hormone secretion (SIADH) occurred. In this study plasma Na and FeNa did not change significantly in SSRI overdose.

The other result of the study was a reduction in plasma PO_4 at 12 and 24 h and also a negative dose-dependent relationship between plasma paracetamol and plasma PO_4, and renal threshold phosphate concentration (TmP/GFR) at 4 h post-ingestion. This finding was consistent with the results of other studies investigating renal loss as a source of hypophosphataemia after paracetamol poisoning [198;199]. Hypophosphataemia due to a decrease in renal threshold phosphate concentration in the early stage of toxicity has been suggested as an early marker in determining the severity of paracetamol toxicity.

Because no patients developed significant renal dysfunction the utility of urinary excretion of electrolytes in predicting specific renal toxicity could not be assessed and studies in patients with this outcome are required.

2-5: Summary

In conclusion paracetamol overdose is associated with a kaliuresis, and a reduction in plasma K which is related to the dose ingested and is of relatively short duration, not longer than 24 h post-ingestion in this study. This suggests a specific renal effect of paracetamol in overdose. These findings might be consistent with increasing aldosterone action on the distal tubules as a fall in renal perfusion due to paracetamol-induced renal vasoconstriction consequent upon cyclo-oxygenase inhibition, (and hence reduced production of vasodilator prostaglandins) activates the renin-angiotensin-aldosterone system. Measurement of aldosterone and plasma rennin activity (PRA) in the future studies may give us a better understanding of renal effects of paracetamol overdose. None of cases developed significant renal impairment. It is therefore uncertain whether these effects are directly related to the renal failure seen occasionally in paracetamol overdose.

2-6: Limitation of the study

Due to the nature of the retrospective study, it was not possible to obtain precise information from patients, and the information recorded in the patient notes was used. As the study required having two sets of biochemistry tests in order to investigate the changes in plasma electrolytes, only those cases that had at least two sets of data were included. This means that the subjects were not necessarily representative of the whole population, particularly at lower doses of paracetamol.

In the prospective study due to nature of the subjects not all cases were able to comply with all blood and urine collections. As routine drug screening for drugs of abuse would not have detected non-steroidal presence and since the complete screen of this nature would be extremely expensive, a full drug screen to rule out co-ingestion of other drugs in the paracetamol group was not performed. Cases of mixed overdose were excluded by patient interview, however, it would have been more likely that co-ingestion to confound and reduce the power of the data and statistical analysis rather than increase it giving us the positive result observed. The precise effect of 5% dextrose and NAC itself was not clear, but the intention was not primarily to examine this. The effects of paracetamol seen appear independent of NAC administration.

Chapter III: Frequency of Renal Injury in Significant Paracetamol Poisoning and the Impact of Severity of Renal Dysfunction on Outcome

3-1:Introduction

Paracetamol poisoning is responsible for around 200 deaths annually in the United Kingdom alone [43;51;268;269]. High doses of paracetamol are capable of causing hepatic necrosis and renal tubular necrosis [18;81;85;164]. Renal failure is less common than liver failure after paracetamol overdose, and has been reported in about 1% of all patients and reaches 8.9-10% in severe poisoning [18;91;270]. The occurrence of renal failure is greater in severely poisoned patients, and is often observed in those that develop significant liver injury [81;271]. Nonetheless, the occurrence of renal failure cannot be attributed solely to co-existent hepatic damage, and has been reported as an isolated manifestation of paracetamol toxicity [87;89;183].

Renal injury, as evaluated by plasma creatinine (Cr) concentrations, may be used to indicate the severity of paracetamol poisoning, and concentrations greater than 300 µmol/l are part of the King's College (KCH) Criteria (arterial pH < 7.3 or all three of an international normalised ratio [INR] of greater than 6.5, plasma Cr > 300 µmol/l and the presence of encephalopathy of grade III or IV for liver transplantation) [54;227]. Despite this, comparatively little is known about the prognostic value of plasma Cr concentrations in patients referred to liver units after severe poisoning.

The present study was designed to examine the frequency of renal injury in patients with severe paracetamol poisoning. The aim was to identify the possible impact of renal impairment on clinical outcomes in this high-risk patient group, and risk factors associated with the development of renal failure in this selected group. Additionally, the effects of significant paracetamol overdose on plasma electrolytes in patients who developed hepatic damage was also investigated.

The specific questions asked were:

1. What is the frequency of renal insufficiency in severe paracetamol overdose?
2. Is the timing of onset of renal dysfunction different from liver dysfunction?
3. What is the effect of delay at first presentation on outcome?
4. What are the associated risk factors in developing kidney dysfunction in paracetamol overdose?
5. What is the impact of Cr at first admission on outcome?
6. What is the effect of paracetamol overdose on serum electrolytes in this selected population?

3-2: Methods

3-2-1: Data Collection

The Scottish Liver Transplant Unit (SLTU) is a tertiary referral centre for Scotland and part of Northern Ireland, and provides clinical management of

patients with severe liver disease and patients that require liver transplantation. Patients were identified from a database held within the SLTU that contains clinical and laboratory variables and outcome data for patients referred to the Unit. Patients referred to the SLTU between 1992 and 2004 inclusive due to severe paracetamol-induced liver damage were included. Available data at the time of initial referral to SLTU included age, gender, other medication ingested, stated dose ingested, associated alcohol, unit of ingested alcohol, interval between ingestion and presentation to hospital, plasma paracetamol concentration, the presence of hypotension (systolic blood pressure <100 mmHg), plasma Cr, alanine transaminase (ALT) activity, gamma glutamyl transpeptidase (GGT) activity, prothrombin time (PT), plasma sodium (Na), potassium (K), bicarbonate (HCO_3) and pH at time of admission to referring hospital and to SLTU. Additional data were worst recorded PT, and outcome data: liver transplant, haemodialysis, intensive care unit (ITU) admission and death. Admission to ITU was determined by necessity for ventilation. Patients with poor prognosis were identified according to the KCH Criteria.

3-2-2: Data Analyses

Ingestion of paracetamol at a single time-point or within a two-hour period was considered as an acute ingestion, whereas ingestion at multiple time-points during an interval of more than two hours was considered a staggered overdose.

Two time points were recorded in patients with acute ingestion of paracetamol. Time from ingestion to first blood taken in referring hospital was considered as interval between ingestion and first admission (or delay at first admission) and time point from ingestion to first blood taken in SLTU was considered as interval between ingestion and admission to SLTU (or delay at admission to SLTU). Patients were categorised into four groups according to interval between overdose and first presentation to referring hospital: ≤12h, >12h to 24 h, >24h to 48 h, and >48 h. For some analyses this interval was classified into three groups: ≤24h, >24-48h and ≥48h.

Renal function was classified into four groups according to plasma Cr concentration: normal: if Cr<120 μmol/l; mild impairment: if Cr>120≤180 μmol/l; moderate impairment: if Cr>180 and <300 μmol/l; and severe impairment: if Cr≥300 μmol/l. The effect of different risk factors was examined in these groups.

Liver dysfunction was defined as PT≥25 (s). Worst PT was defined as worst recorded PT over hospital stay either in referring hospital or in the SLTU.

In the previous studies reported in this thesis (chapter II) the effect of acute paracetamol overdose on electrolytes was investigated. In the current data, the effects of acute severe paracetamol overdose on plasma electrolytes, sodium (Na) and potassium (K), in the subset of patients with acute paracetamol overdose (n=361) presenting at different times after ingestion was examined. In

this analysis patients were categorised in three groups according to the time between ingestion and first presentation to the hospital (or the time of first blood taken in referring hospital): group 1: ≤12h; group 2: >12h to 24h; and group 3: ≥24h. In this subset, the relationships between plasma K, paracetamol, Cr and PT at first admission to hospital were also examined.

3-3: Statistical analyses

Data was tested for normality. The data are presented as mean ± standard error of the mean (sem), median and inter quartile range (IQR), and proportions where appropriate. Between-group comparisons were made using Student's t test for independent samples for continuous data, and Pearson's Chi square tests for categorical data. Multiple comparisons analysis for continuous data was made by one-way analysis of variance (ANOVA) with Post-Hoc Bonferroni for parametric data and Kruskal-Wallis test for non-parametric data. Receiver operator characteristics (ROC) were used to examine the relationship between Cr concentration at the time of admission to referring hospital and end-point of prognosis defined by KCH criteria (when mortality was also used as the end-point, the same result was obtained).

To determine risk factors of renal dysfunction initially univariate analysis was performed. In the second step multiple regression analysis was applied, however, the model automatically excluded patient with "staggered overdose"

because time between ingestion and admission was unknown in this group. As this group was found to be an important risk factor in the univariate analysis, use of multiple regression was thought likely to be unreliable. The results from the univariate analysis are therefore presented.

3-4: Results

3-4-1: Demographic characteristic

Data was available for 522 patients (49.2% men and 50.8% women) with mean age of 36 ± 1 y. In younger patients (<20 y) overdose was more common among women, but in older patients (>40 y) overdose was more frequent in men (Figure and Table 3.1) (see appendix 3.1 for raw data).

Figure 3.1: Distribution of patients with overdose according to sex and age bands.

AGES BANDS	sex		Total
	male	female	
11-20 YEARS	11	28	39
21-30 YEARS	81	95	176
31-40 YEARS	68	69	137
41-50 YEARS	59	53	112
51-60 YEARS	26	10	36
61 AND OLDER	12	10	22
Total	257	265	522

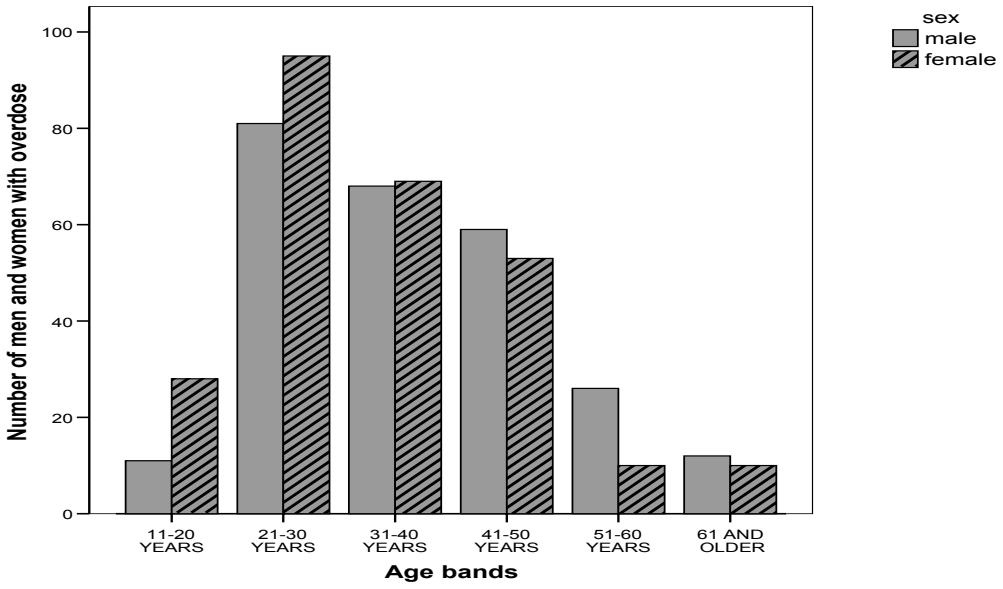


Table 3.1: Demographic characteristic of subjects with paracetamol overdose (n=522) with suspected liver damage referred to SLTU at admission to the referring hospital.

• Total n (%)	522 (100%)
• Gender	
Male	257 (49.2%)
Female	265 (50.8%)
• Age y (mean ±sem)	35.6 ± 0.6
Male	37.2 ± 0.8
Female	34.1 ± 0.8
• NAC treatment	
Yes n (valid %)	431 (84.5%)
NO n (valid %)	79 (15.5%)
Missing data n	5
• Staggered overdose	
Yes n (valid %)	128 (26.6%)
NO n (valid %)	354 (73.4%)
Missing data	40
• KCH poor prognosis	
Yes n (%)	145 (27.8%)
NO n (%)	377 (72.2%)
• Dialysis requirement	
Yes n (valid %)	177 (34.2%)
NO n (valid%)	341 65.8%)
Missisng data n	4
• Mortality	
Died without transplant n (%)	134 (25.7%)
Died with transplant n (%)	13 (2.5%)
Survived without transplant n (%)	347 (66.5%)
Survived with transplant	28 (5.4%)

3-4-2: Frequency of renal insufficiency

At first presentation to the referring hospital 463 patients had available data for plasma Cr and PT of whom 320 (69.1%) had significant impairment of liver function as reflected by PT at first admission ≥25 (s) (Table and Figure 3.2). Of patients who had liver injury, 156 (48.8%) had already developed some degree of renal dysfunction. Of these, 69 patients had mild, 48 patient moderate, and 39 patients severe renal injury. At presentation to the referring hospital 143 patients did not have significant liver impairment (PT at first admission< 25), but 26 cases had some degree of renal dysfunction (17 mild, 7 moderate and 2 severe). All of these 26 patients showed some degree of abnormal liver function, although not achieving a PT of ≥25, concomitant with their renal dysfunction (see appendix 4-2 for raw data). At the time of first admission to hospital, in the total cohort, 18.6% (86/463) had mild, 11.9 % (55/463) moderate and 8.9 % (41/463) severe renal impairment (Table 3.2).

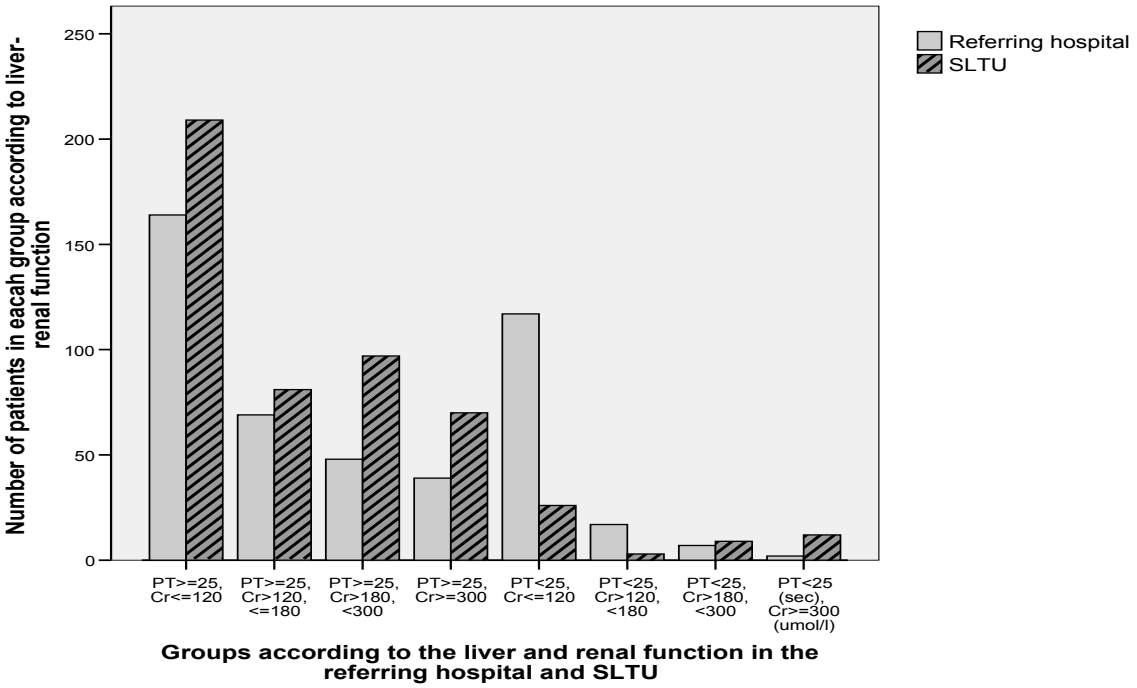
At the point of admission to the SLTU, 507 subjects had available data for PT and Cr. Of these 457 (90.1%) had significant liver damage as defined by plasma PT at admission to SLTU ≥25 (s) (Table and Figure 3.2). Of those with liver injury more than half of patients (248/457) had renal dysfunction: 17.7% (81/457) mild, 21.1% (97/457) moderate, and 15.3% (70/457) severe renal dysfunction as defined by plasma Cr at admission to SLTU.

Table 3.2: Severity of liver and renal impairment at presentation to referring hospital (first admission) and SLTU.

Patients were classified according to the severity of renal dysfunction and presence or absence of liver damage. Liver injury was defined as PT>=25 sec. Renal injury was defined as normal if plasma Cr ≤120; mild: Cr >120, ≤ 180; moderate: Cr >180, <300; severe: Cr≥ 300 µmol/l. PT: prothrombin time (sec), Cr: creatinine (µmol/l). n=number of subjects with available data.

Groups according to renal and liver function	Referring hospital (n=463)		SLTU (n=507)	
	PT≥25 (with liver injury)	PT<25 (no liver injury)	PT≥25 (with liver injury)	PT<25 (no liver injury)
	n (%)	n (%)	n (%)	n (%)
Normal renal function Cr≤120	164 (35.4%)	117 (25.3%)	209 (41.2%)	26 (5.1%)
Mild renal dysfunction Cr >120, ≤180	69 (14.9%)	17 (3.7%)	81 (16.0%)	3 (0.6%)
Moderate renal dysfunction Cr >180, <300	48 (10.4%)	7 (1.5%)	97 (19.1%)	9 (1.8%)
Severe renal dysfunction Cr ≥300	39 (8.4%)	2 (0.4%)	70 (13.8%)	12 (2.4%)
Total	320 (69.1%)	143 (30.9%)	457 (90.1%)	50 (9.9%)

Figure 3.2: Severity of liver and renal impairment at presentation to referring hospital (first admission) and SLTU.



3-4-3: Timing of onset of renal and liver dysfunction

Changes in liver function occurred more rapidly than those in renal function. Thus PT (s) and ALT (IU/l) were generally abnormal at initial presentation in all patients, although higher in those who presented at more than 24 h after overdose (PT: 50.8 ± 2.4 (s), ALT: 6227 ± 454 (IU/l)) compared to those presented within 24 h (PT: 29.9 ± 1.7 (s), ALT: 1960 ± 264 (IU/l)), $p<0.0001$ (Table 3.3).

Changes in renal function occurred later after overdose (>48h). Cr concentrations (μmol/l) at first admission were significantly higher in patients presenting more than 24 h after ingestion (155.8 ± 7.9 μmol/l) whereas patients who presenting within 24 h often had a normal Cr (98.3 ± 3.7 μmol/l), $p<0.0001$ (Table 3.3). Cr in the group that presented after 48 h (192.6 ± 18.2 μmol/l) was significantly higher than that in the group presenting between >24 and 48 h (140.6 ± 7.9 μmol/l), $p<0.0001$. Cr at first admission (μmol/l) in staggered overdose was 177.9 ± 12.0 μmol/l). There was no age difference between groups presenting within (32.5 ± 0.9 y) or after 24 h (34.6 ± 1.0 y).

3-4-4: Effect of delay at first admission on outcome

Mortality rates were highest in patients first presenting to hospital more than 24 h after ingestion ($p<0.01$) and after staggered overdose (Table 3.3, Figure 3.3). A prolonged interval between paracetamol ingestion and first presentation to hospital (>24h) was also associated with an increase in proportion having poor prognosis based on KCH and dialysis requirement (Table 3.3, Figure 3.4). Thus in the group who presented after 24 h, 33.6% (49 of 146) had poor prognosis criteria as compared to 17.6% (31/176) in patients presenting within 24 h, $p<0.01$ (Table 3.3). Mortality in the group with staggered overdose was significantly worse [34.4% (44/128)] than in those with acute overdose [21.5% (76/354)], $p<0.01$.

Table 3.3: Laboratory and clinical variables with respect to the interval between acute paracetamol ingestion and first blood taken at first admission to hospital in paracetamol overdose, presented as mean± sem.

Group comparison was made using ANOVA with post-Hoc Bonferroni for continuous data and Pearson Chi-square test for categorical data. n=number of subjects with available data. KCH: King's College Criteria.

Time between ingestion and first blood taken at first admission to referring hospital	**≤24h**	**>24 ≤48h**	**>48h**	**Sig level**
Interval (h)	15.2 ± 0.5 (n=176)	37.4 ± 0.8 (n=104)	66.6 ± 2.8 (n=42)	
Cr at first admission (µmol/l)	98.3±3.7(n=161)	140.6±7.9 (n=94)	192.6±18.2 (n=39)	p<0.0001 [a]
PT at first admission (s)	29.9±1.7 (n=166)	45.4±2.1 (n=101)	65.0±6.0 (n=39)	p<0.0001 [a]
ALT at first admission (IU/l)	1960±264 (n=147)	5524±520 (n=75)	7887±875 (n=30)	p<0.0001 [b]
Worst PT (s)	62.8±2.9 (n=173)	67.3±3.4 (n=104)	77.1± 6.4 (n=42)	NS
Dialysis (%)	19.5 (n=34/174)	44.2 (n=46/104)	34.1 (n=14/41)	p<0.0001 [c]
KCH poor prognosis (%)	17.6 (n=31/176)	36.5 (n=38/104)	26.2 (n=11/42)	p<0.01 [d]
Mortality (%)	15.3 (n=27/176)	28.3 (n=30/104)	23.8 (n=10/42)	P<0.05 [d]

[a] Plasma Cr and PT was significantly different between groups (p<0.0001). Those presenting less than 24h were different to those presenting later (p<0.0001). Cr and PT was also significantly higher in the group who presented more than 48h compared to group presenting >24-48h (p<0.0001).

[b] ALT was higher in patients presenting >24h (p<0.0001) compared to groups presenting within 24h. ALT was also higher in >48h group compared to >24 to 48h group (p<0.05).

[c] Dialysis requirement was significantly higher in patients presenting >24h compared to group presenting <24h (p<0.0001).

[d] KCHC poor prognosis and mortality were significantly higher in patients presenting more than 24h compared to those presenting within 24h (p<0.01 for KCHC poor prognosis, p<0. 05 for mortality).

Figure 3.3: Survival according to time between ingestion and first admission to the hospital.

Morality was significantly higher in the group presented after 24 h and in staggered overdose (missing data: 72).

Groups according time between ingestion and first presentation and staggered overdose	Survival		Total
	survived	Died	
<=12 h	54	5	59
>12<=24 h	95	22	117
>24<=48 h	74	30	104
>48 h	32	10	42
Staggered OD	84	44	128
Total	339	111	450

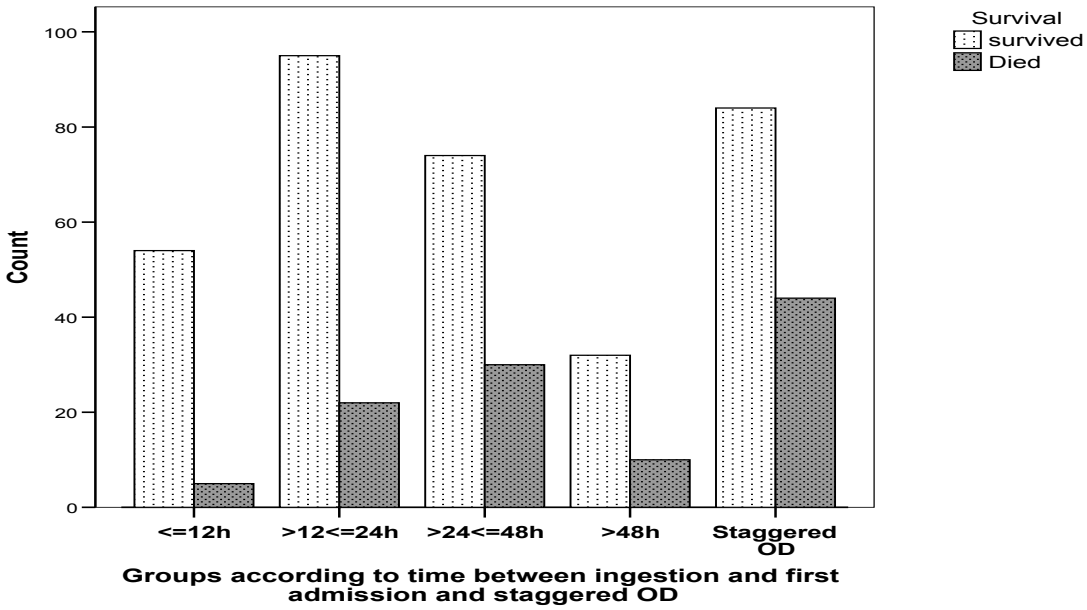
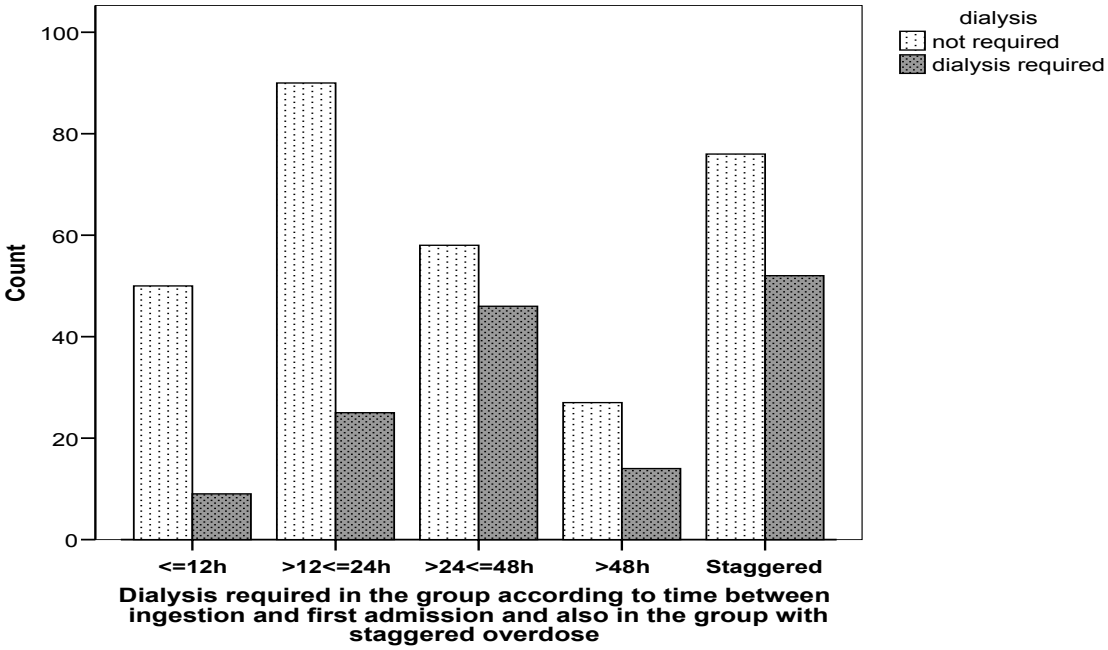


Figure 3.4: Dialysis requirement according to time between ingestion and first admission to the hospital (missing data: 75).

Groups according to time between ingestion an first admission and staggered overdose	dialysis		Total
	not required	dialysis required	
<=12 h	50	9	59
>12<=24 h	90	25	115
>24<=48 h	58	46	104
>48 h	27	14	41
Staggered overdose	76	52	128
Total	301	146	447



Overall, 96.6% of patients developed significant liver injury (worst PT ≥25 s). Data on the highest Cr during in-patient stay was not available; however, 34.2% of patients (177) required dialysis, and 27.8% (145) had poor KCH criteria. Overall mortality was 28.2% (147) (Table 3.1).

Stated paracetamol dose in acute ingestions did not correlate with risk of renal impairment as judged by Cr at time of admission to SLTU (Cr ≤120 μmol/l: paracetamol 34 ± 2 g; Cr>120 and ≤180 μmol/l: paracetamol 28 ± 2g; Cr >180 and <300 μmol/l: paracetamol 39 ± 3 g; ≥300 μmol/l: paracetamol 27 ± 3 g). There was no significant difference in the stated dose of ingested paracetamol in the group with acute and staggered overdose (staggered overdose: 30 ± 2.3 g vs. acute overdose: 33.5 ± 5 g).

3-4-5: Associated risk factors for developing renal dysfunction

Factors associated with more severe renal impairment at the time of transfer to SLTU were age, hypotension at admission to either hospital, and interval between ingestion and first presentation to hospital (all $p<0.0001$). Patients with more severe renal injury (defined by Cr at presentation to SLTU) also had a higher GGT and PT at first presentation (Table 3.4 and Figure 3.5 and 3.6, $p<0.0001$). There was no statistically significant association between severity of renal impairment with weekly alcohol intake or associated alcohol ingestion with overdose. Patients with more severe renal dysfunction were more acidotic and

hyperkalaemic (Table 3.4). A higher proportion of patients with severe renal impairment had taken a staggered overdose, compared to acute overdose (Table 3.4). The data showed that males were more likely to develop renal dysfunction ($p<0.05$), however this was confounded by age as men were significantly older than women (male: 37.2 ± 0.8 y vs. female: 34.1 ± 0.8 y, $p<0.01$).

Figure 3.5: Relationship between PT (Sec) at first admission to referring hospital and creatinine (µmol/l) at admission to SLTU.

There was significant positive association between PT at first admission and creatinine at admission to SLTU ($r=0.22$, $n=465$, $p<0.0001$).

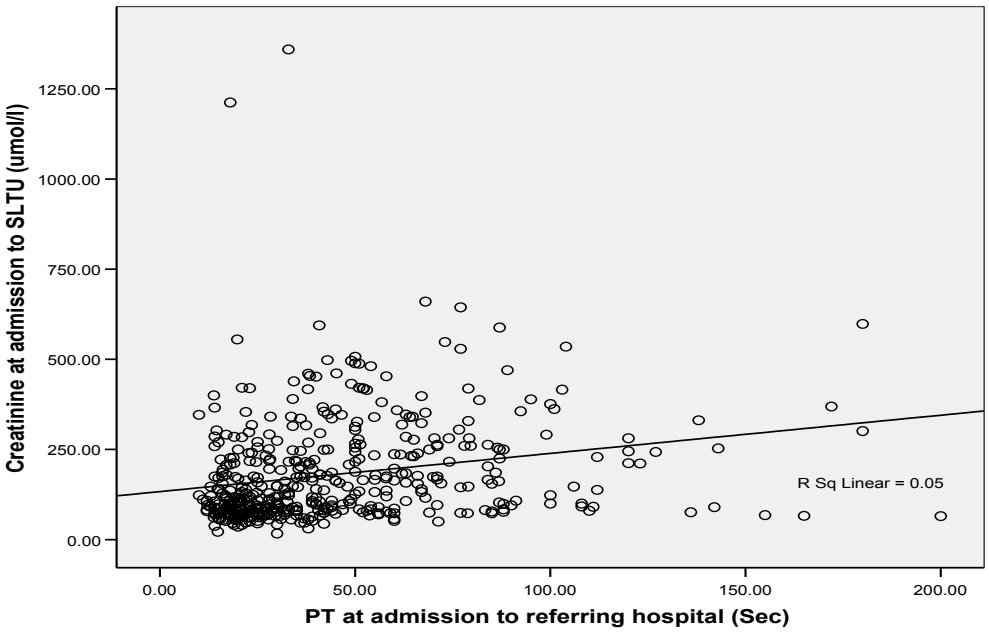


Table 3.4: Clinical characteristics and outcomes in patients with paracetamol overdose grouped by renal function (see text) at the time of admission to SLTU.

Group comparison was made using ANOVA with post-Hoc Bonferroni for continuous variables and Chi-square test for categorical variables. n=number of subjects with available data.

Cr (μmol/l) at admission to SLTU	**Normal ≤120**	**Mild >120 and ≤ 180**	**Moderate >180 and <300**	**Severe ≥300**	**Sig. level**
n (%)	239 (46.8%)	84 (16.4%)	106 (20.7%)	82 (16.0%)	
M / F	102/137	45/39	62/44	42/40	
Age (y)	32 ± 1	38 ± 2	39 ± 1	39 ± 1	p<0.0001 [a]
Staggered overdose (%) (n=Yes/total)	18.5% (n=43/233)	28.5% (n=22/78)	26.9% (n=25/93)	50.7% (n=36/71)	P<0.0001 [b]
Alcohol intake (Unit per week)	56.2 ± 7.02 n=149	86.5 ± 15.8 n=58	90.8 ± 13.3 n=76	78.3 ± 16.0 n=70	P=0.08
Associated alcohol (n=Yes/total)	87/212	38/77	47/90	4/67	P=0.22
Hypotension at first admission (%)	3.9% (n=9/239)	18.1% (n=15/83)	32.0% (n=33/103)	32.1% (n=25/78)	p<0.0001 [c]
Delay to first admission (h)	25 ± 1 (n=179)	28 ± 2 (n=56)	36 ± 3 (n=65)	43 ± 5 (n=37)	p<0.0001 [d]
Delay to admission to SLTU (h)	55 ± 2 (n=158)	55 ± 3 (n=51)	59 ± 2 (n=56)	68 ± 5 (n=33)	p<0.05 [e]
PT at first admission (s)	37 ± 9 (n=211)	42 ± 2.8 (n=77)	51 ± 3.2 (n=92)	59 ± 4 (n=75)	P<0.0001 [f]
GGT at first admission (u/l)	82 ± 8 (n=144)	155 ±19 (n=57)	164 ± 18 (n=57)	238 ±24 (n=51)	p<0.0001 [g]
$[H^+]$ at first admission (mmol/l	42 ± 1 (n=149)	53 ± 3 (n=58)	61 ± 4 (n=64)	54 ± 3 (n=54)	p<0.0001 [h]
K at first admission (mmol/l)	3.9 ± 0.05 (n=222)	4.2 ± 1.0 (n=75)	4.5± 1.0 (n=100)	4.8± 0.1 (n=73)	p<0.0001 [i]
Worst PT (sec)	59±2 (n=235)	73 ± 5 (n=84)	82 ± 5 (n=106)	75 ± 5 (n=81)	p<0.0001 [k]
ITU stay (days)	1.4 ± 0.2 (n=237)	2.5 ± 0.4 (n=83)	4.7± 1.0 (n=104)	4.1 ± 0.6 (n=80)	p<0.0001 [m]
Mortality (%)	8.8 (n=21/239)	32.1 (n=27/84)	47.2 (n=50/106)	51.2 (n=42/82)	p<0.0001 [n]

Foot notes for Table 3.4

[a] Patients with mild, moderate and severe renal dysfunction were older ($p<0.0001$). Those with moderate and severe renal dysfunction were older than those with mild renal dysfunction ($p<0.0001$).

[b] Patients with severe renal dysfunction were more likely to take staggered overdose compared to normal renal function ($p<0.0001$), and mild or moderate renal dysfunction ($p<0.01$).

[c] Patients with normal renal dysfunction were less likely to have hypotension at first admission compared to other groups ($p<0.0001$).

[d] Patients with moderate and severe renal dysfunction presented later than those with normal renal function ($p<0.0001$). Patients with severe renal dysfunction presented later than patients with mild renal dysfunction ($p<0.01$).

[e]Time from overdose to admission to SLTU was significantly longer in the group with severe renal dysfunction compared to group with normal renal function ($p<0.05$).

[f] There was significant difference in first admission PT between groups ($p<0.0001$). PT at first admission in those with normal renal function was lower than moderate and severe renal dysfunction ($p<0.01$). Referral PT in mild and severe renal dysfunction was also significantly different ($p<0.01$).

[g] GGT at first admission was lower in patients with normal renal function ($p<0.0001$). GGT at first admission was higher in severe than mild ($p<0.01$) or moderate ($p<0.05$) renal dysfunction.

[h] $[H^+]$ at first admission in the group with normal renal function was significantly different to mild ($p<0.01$), moderate ($p<0.0001$) and severe ($p<0.01$) renal dysfunction.

[i] K^+ at first admission in the group with normal renal function was significantly lower than moderate and severe renal dysfunction ($p<0.0001$). K^+ at first admission in mild renal dysfunction was significantly lower than severe renal dysfunction ($p<0.0001$).

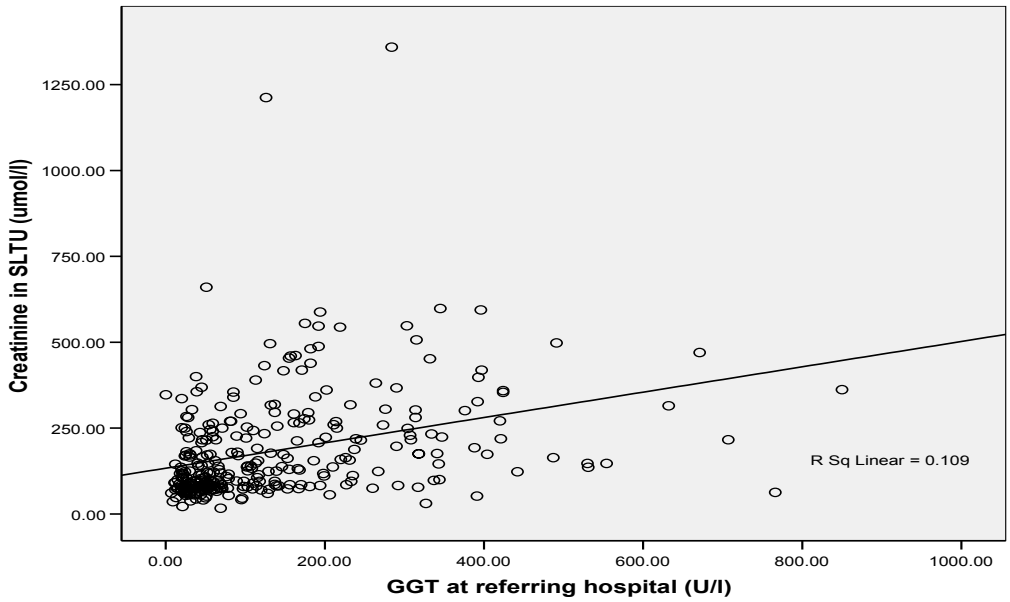
[K] Worst PT in normal group was significantly different between group with mild ($p<0.05$), moderate ($p<0.0001$) and severe renal dysfunction ($p<0.05$).

[m] Patients with moderate and severe renal dysfunction stayed longer in the intensive care unit (ITU) compared to group with normal renal function ($p<0.0001$, and $p<0.01$, respectively).

[n] Mortality in the group with normal renal function was significantly lower compared to the group with mild, moderate and severe renal dysfunction ($p<0.0001$). Group with mild renal dysfunction had lower mortality compared to the group with moderate and severe renal dysfunction ($p<0.05$).

Figure 3.6: Relationship between GGT (U/l) at first admission to referring hospital and creatinine (μmol/l) at admission to SLTU.

There was significant positive association between GGT at first admission and creatinine at admission to SLTU (r=0.33, n=309, p<0.0001).

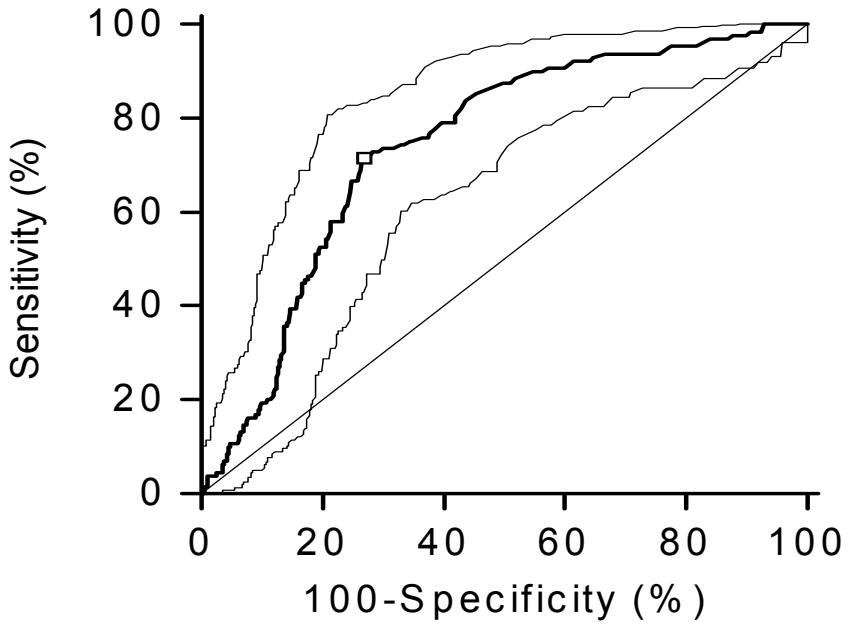


3-4-6: Creatinine at first admission as a prognostic factor

The ROC curve for Cr concentration at first admission as predictor of poor prognosis based on KCH criteria gave an area under the curve of 74.3.0% (95% confidence interval 70.1 to 78.1%, p <0.0001). This plot indicated that a Cr >123 μmol/l at first presentation to the hospital had a sensitivity of 71.3% (95% CI: 62.7-78.9%) and specificity of 73.3% (95% CI: 68.3-77.9%) for poor prognosis defined by KCH criteria during hospital stay (Figure 3.7).

Figure 3.7. Receiver operating characteristic (ROC) for creatinine concentration (μmol/l) at first admission to referring hospital and the end point of poor prognosis according to "King's College Criteria" (KCH).

Area under the ROC curve (AUC) = 74.3% (95% Confidence interval 70.1 to 78.1%) Significance level p< 0.0001 (versus 0.5 line by z-test). Most 'accurate' predictor is referral creatinine >123 μmol/L 71.3% sensitivity (95% CI: 62.7-78.9) and 73.3% specificity (95% CI: 68.3-77.9) (□ point in the graph). Dashed curve lines represent 95% confidence interval lines.



3-4-7: Effect of acute paracetamol overdose on plasma electrolytes

The number of patients with acute paracetamol overdose and known time of ingestion who were entered into this analysis was 316, 49.4% (n=156) male and 50.6% (n=160) female, with mean age of 32.2 ± 0.7 y (Table 3.5). Median and IQR of time interval between ingestion and first admission in the groups presenting within 12 h (group 1, n=59) was 8.0 (6.0-11.0) h; in the group with >12 and ≤24 h (group 2, n=115) 18.0 (16.0-22.0) h; and in the group with >24 h (group 3, n=142): 44.0 (33.0-52.0) h. As expected plasma

paracetamol (mg/l) at first admission was significantly higher in the groups presenting earlier (group 1: 166.3 [83.1-266.5], n=53; group 2: 90.7 [42.0-151.2], n=103; group 3: 37.8 [14.4-93.1 n=117], p<0.0001). There was no significant different in plasma K in the groups presenting within 12 or 24 h (≤12 h: 3.7 [3.3-4.2] mmol/l, n=53 and >12 and ≤24 h: 3.9 [3.4-4.4] mmol/l, n=108), but plasma potassium was significantly higher (4.5 [3.8-5.0] mmol/l, n=133) in patients presenting after 24h than those admitted earlier (p<0.0001).

Plasma K at first admission in the group presenting within 12 h was in a borderline significant negative correlation with plasma paracetamol (r = - 0.28, p=0.05, n=49, Figure 3.8) and did not correlate to Cr or PT at first admission. In patients presenting after 12 h plasma K was significantly positively correlated with plasma Cr (r=0.37, n=225, P<0.0001, Figure 3.9), PT (r = 0.38, n=237, p<0.0001) and plasma [H^+] (r = 0.28, n=163, p<0.0001), but not with plasma paracetamol concentration.

There was no significant correlation between plasma sodium and Cr or PT at first admission. Plasma [H^+] (mmol/l) at first admission was significantly lower in the group with normal renal function than groups with renal dysfunction (p<0.01) (Table 3.5).

Table 3.5: Demographic characteristic of subjects with acute paracetamol overdose (n=316) with suspected liver damage at admission to the referring hospital in the groups according to time interval between ingestion and first admission to the hospital.

Group 1: ≤12 h; group 2: >12 h and ≤24 h; group 3: >24 h. There was significant difference between groups in respect of plasma paracetamol concentration, ALT, PT, Cr and K in the groups presented to the hospital in different time after ingestion. Plasma paracetamol concentration was significantly higher in the group presented earlier ($p<0.0001$). Plasma ALT, PT, Cr and K was significantly higher in the group presented after 24 h compared to those presented before 24 h ($p<0.0001$). There was no significant difference in plasma PT, Cr and K in the group presenting within 12 or 24 h after ingestion. Plasma ALT was slightly higher in the group admitted after 12 h compared to the that of group 2, $p<0.05$. Data was presented as median and IQR. Group comparison was made by Kruskal Wallis test. *: $p<0.0001$, **: not significant. n=number.

Variables/groups	≤12h	>12 h and ≤24 h	> 24 h
Number	59	115	142
Interval (h)	8.0 (6.0-11.0)	18.0 (16.0-22.0)	44.0 (33.0-52.0)
Sex (M/F)**	26/33	54/61	76/66
Age (y) **	30.0 (24.0-41.0)	30.0 (23.0-37.0)	34.0 (24.0-43.0)
Para (mg/l)*	166.3 (83.1-266.5), n=53	90.7 (42.0-151.2), n=103	37.8 (14.4-93.1), n=117
ALT (IU/L)*	443 (1770-2100), n=51	878 (409-1785), n=94	5748 (2126-9233), n=104
PT (sec)*	22.5 (16.1-35.8), n=52	22.9 (19.0-31.8), n=112	42.8 (31.5-63.5, n=137
Cr (µml/l)*	85.0 (75.0-101.0), n=55	90.0 (74.3-110.3), n=104	124.0 (92.0-189.0), n=130
K (mmol/l)*	3.7 (3.3-4.2), n=53	3.9 (3.4-4.4), n=108	4.5 (3.8-5.0), n=133
H^+(mmol/l)**	39 (37-43), n=31	39.8 (35.5-47.5), n=77	41.4 (36.0-53.6), n=94

Figure 3.8: Relationship between referring plasma potassium (mmol/l) and paracetamol concentration (mg/l) in the group presenting within 12 h post-ingestion.

There was borderline reverse association between plasma potassium and paracetamol concentration in the group presenting within 12 h post-ingestion (r= -0.28, n=49, p=0.05).

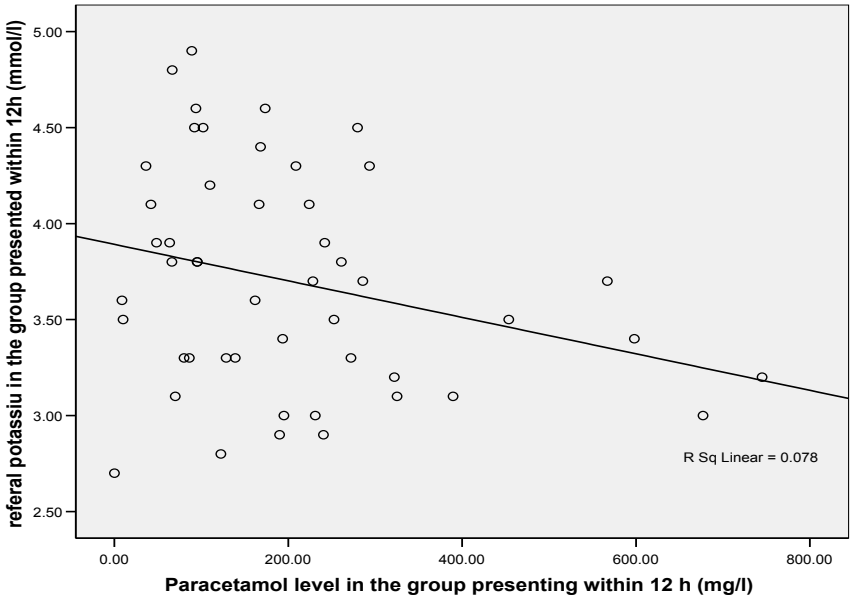
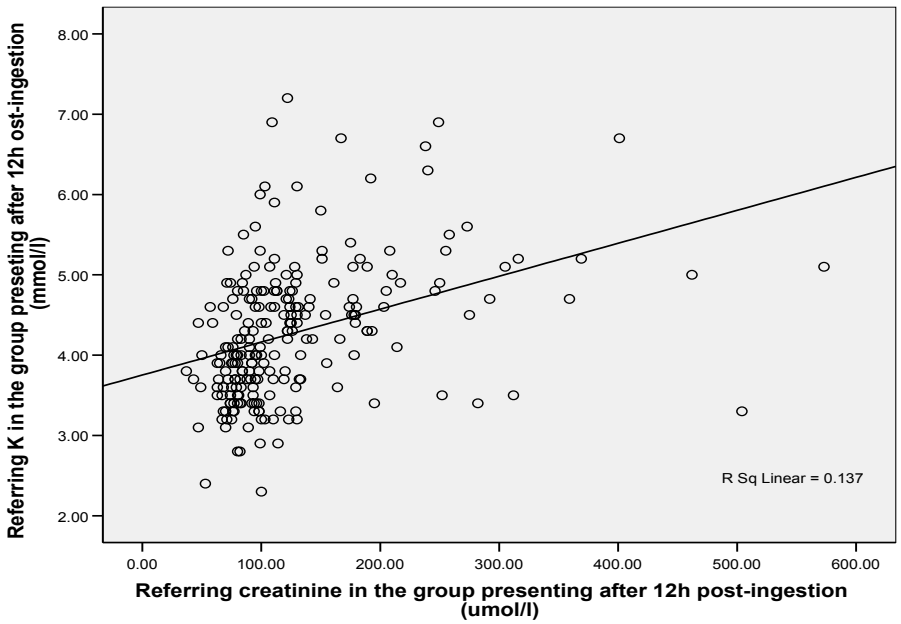


Figure 3.9: Relationship between plasma potassium (K) and creatinine in the group presenting after 12 h post-ingestion.

There was significant positive association between potassium and creatinine in the group presenting after 12 h post-ingestion (r=0.37, n=225, p<0.0001).



3-5: Discussion

Paracetamol poisoning is a common presentation and early identification of patients with more severe poisoning is key to improving outcomes. Present approaches are based on risk stratification using paracetamol concentrations timed after ingestion, but this is dependent on accurate history and assumes an acute ingestion time point. This is also less accurate beyond 15 h after ingestion. Thus, work that is aimed to improve outcome prediction based on paracetamol concentrations [272] may not be applicable to many in this cohort. Previous work has identified acidosis and hypophosphataemia as potential early markers of more severe toxicity [198]. Patients in this cohort often did not have phosphate measured and this has not been a focus of this study.

Although renal failure is a recognised complication of paracetamol toxicity, the underlying mechanisms are poorly understood. Toxic metabolites of paracetamol are generated by local metabolism in the kidney and may cause acute tubular necrosis, particularly in conditions associated with glutathione depletion [168]. Even in the absence of acute renal failure, paracetamol ingestion is associated with dose-dependent changes in electrolyte transport, suggesting a direct pharmacological action of paracetamol on renal tubular function [194;273]. Risk factors such as glutathione depletion in the kidney, concomitant ingestion of nephrotoxic substances, dehydration at presentation, chronic excessive overdose of paracetamol, and pre-existing

liver and renal insufficiency have been suggested to promote the risk of renal injury after paracetamol overdose [183].

As expected, most patients in the current series of tertiary referrals after paracetamol overdose had evidence of acute liver dysfunction defined by PT ≥ 25 sec (96.6%). Within this patient population there was a high prevalence of serious renal impairment (34.2% of patients required dialysis). In comparison the incidence of paracetamol-induced nephrotoxicity (blood urea nitrogen>6.4 mmol/l, or Cr>97.2 µmol/l) in adolescents (12-18y) who were admitted to a tertiary hospital was reported to be 8.9% [270]. In the current study 15.4% (6/39) of patients aged 11-20y had Cr≥120 µmol/l and 13% (n=5) required dialysis. The overall incidence of paracetamol-induced nephrotoxicity in unselected patients has previously been reported to be around 1-2 % rising to 10% in more severely poisoned patients [18;91;274]. The high incidence of renal impairment in the current study is likely to be due to the highly selected patient population, who were characterised by liver dysfunction secondary to paracetamol overdose sufficient to warrant referral to a tertiary centre. Severe liver failure itself was found to be an important associated factor in developing renal failure.

As shown in Table 3.3 the onset of renal dysfunction seems to be later than liver dysfunction. Other studies also report liver dysfunction starts within 24 h after overdosage while renal dysfunction occurs one to three days later, and often is in association with severe liver damage [18;42;83;91]. In some

cases, although rare, renal failure due to paracetamol overdose occurs in the absence of liver injury [84;87;90;161;183]. In the current data set all patients with renal impairment also had some degree of concomitant liver dysfunction.

Importantly the data indicate that Cr at the time of first admission was an important predictor of developing poor prognosis (as defined by KCH criteria) and thus the need for liver transplantation (Figure 3.7). Groups with more severe renal injury at presentation had worse outcome, as indicated by higher PT, longer stay in ITU, greater need for dialysis, and higher mortality (Table 3.4).

Renal dysfunction was more severe with later presentations, in patients with hypotension at admission, those who were older and those who had a high GGT. However, in this data set there was no significant association between weekly intake of alcohol or history of alcohol abuse and renal dysfunction. Renal dysfunction was also worse in those who had taken the overdose in a staggered manner. The findings of the current study are similar to those in children, in whom prolonged interval between ingestion and presentation to hospital, and renal impairment were both associated with poorer prognosis [275].

Mortality in the current study (28.2%) is lower than that reported in a previous study from another UK tertiary care date set (62% in 1987 and 40% in 1993).

This may suggest an improvement in the quality of care given for this patient group in the UK in the recent years, or be due to changes in referral practice.

The current data comes from a large acute UK centre but may not be representative of other liver units. Other factors not tested in this study include social deprivation, which has also been found to be associated with poor outcome from paracetamol overdose in Scotland [276]. The use of plasma creatinine needs to be tested independently by others. The present data underpin the importance of prompt administration of acetylcysteine, which has been shown to be most effective when given within the first 8-12 h after paracetamol ingestion [277]. Another study on similar patients admitted to an acute liver unit in the UK showed that patients who were not treated with NAC, or in whom NAC was started after 24h, had significantly higher mortality rate [53]. It is increasingly recognised that patients presenting to hospital after staggered overdose are at substantially increased risk compared to those after acute ingestion. This is reflected in the present data, where staggered overdoses comprise a high proportion of patients referred to the SLTU. Thus close attention to Cr concentration, presence of hypotension and GGT activity should allow earlier identification of patients that are at greater risk of poor outcome.

In the subset of patients with acute (non-staggered) overdose, in the group who presented early (within 12h) plasma K was in a borderline dose-dependent negative relationship with plasma paracetamol. This

finding is similar to the results of previous human and experimental studies [194;198;273] (chapter II of the thesis) in which the effect of paracetamol overdose on plasma electrolytes were investigated. There was no association between plasma paracetamol and plasma K in the group presenting later than 12h. In these patients plasma K was in significant positive relationship with plasma Cr and PT. This suggests relationships between plasma K and plasma paracetamol vary with time after exposure. In the early stages of toxicity fall in plasma K might be associated with higher plasma paracetamol concentrations, and hence ingested dose. Later changes reflect renal injury, either secondary to plasma paracetamol itself or consequent upon liver injury.

3-6: Conclusion

While renal impairment is relatively uncommon after mild to moderate paracetamol overdose [271], it is a common complication in patients referred to a tertiary centre with severe paracetamol toxicity. The timing of onset of renal dysfunction is later than liver injury. Important clinical factors predicting poor outcome were: presentation to hospital after 24 h after ingestion, high Cr concentration at the time of first presentation, hypotension, staggered overdose, raised GGT and concomitant liver dysfunction. Renal dysfunction at first presentation appears an important predictor of subsequent liver toxicity and death. Further work is required to explore whether more subtle markers of renal impairment might allow better risk stratification in patients that present to hospital after paracetamol overdose. The effect of

paracetamol on plasma potassium varies with time after ingestion, suggesting different mechanisms for plasma K change in early and later stage of toxicity. Fall in plasma potassium in the early stage may be due to cyclo-oxygenase inhibitory effects of paracetamol, which alter renal haemodynamics and tubular handling of electrolytes in the kidney. Later changes in plasma K are likely to be due to direct nephrotoxic effects of paracetamol. Measurement of renal effects of paracetamol overdose may allow greater understanding of mechanisms of paracetamol toxicity.

Chapter IV: Liver Admission Following Paracetamol Overdose with Concentration Below Current UK Treatment Threshold

4-1: Introduction

Paracetamol overdose is a major public health problem in the UK and the cause of 40% of all overdose presentations to hospital. Paracetamol overdose is the commonest cause of acute liver failure in the UK [51], resulting in several hundred liver unit admissions and about 200 deaths each year [278;279]. Patients at sufficient risk of hepatotoxicity are treated with the intravenous antidote acetylcysteine (NAC), which has been used as the treatment of choice for paracetamol overdose since 1979 [203]. For patients presenting within 15 hours (h) after ingestion, the need to antidote therapy is determined on the basis of a nomogram which relates plasma paracetamol concentration to the time since ingestion. Patients are stratified depending on their "risk factors" including: chronic alcohol misuse [280], chronic enzyme induction [281], and malnutrition [282]. Those with no risk factors are treated if they have a paracetamol concentration above a line starting at 200 mg/l at 4 h and subject to first-order decline with 4 h half-life (the "200 line"). Those with risk factors of enhanced hepatotoxicity are treated at half these concentrations ("100 line"). If patients are not treated with antidote, more than 60% of patients with plasma paracetamol concentration above the treatment line may develop serious liver damage, and of those about 5% may die [213].

In 1998, 4 cases of fatal hepatotoxicity were reported following paracetamol overdose with plasma concentration below the "200 line". All 4 patients presented within 4-6 h pots-ingestion. None of the cases received antidote therapy initially and in three of four this action was consistent with current UK

guidelines [218]. The authors suggested lowering treatment threshold by 25% to a “150 line” (in the absence of risk factors) to bring them in the line with nomograms used in some other countries, including the US. The report generated much controversy with both support [219] and criticism [220;221;223;224;283]. However, the absolute risk of hepatotoxicity in patients with paracetamol concentration between the 150 and 200 lines has not determined accurately, and it remains unclear whether the benefits of treatment outweigh the risks, or if additional treatment is cost-effective in this group. Consequently, UK treatment guidelines have not been changed.

The current study is a systemic retrospective survey performed in defined geographic areas over specific time periods, to establish the numbers of patients admitted to two liver units with paracetamol-induced hepatic dysfunction who had initial paracetamol concentration below the current nomogram levels at their original presentation.

4-2: Method

The records of all patients admitted to the Scottish Liver Transplant Unit (SLTU) in Royal Infirmary of Edinburgh and regional liver service in Newcastle with paracetamol overdose and liver dysfunction were reviewed. The period of study was from January 1992 to June 2004 for SLTU data and from September 1996 to March 2003 for Newcastle data set. These two services cover a population of 9.0 million people, and therefore the period of

study encompassed about 95 million person-years. Data in Edinburgh and Newcastle were separately extracted, and amalgamated.

Details of all patients were recorded at the time of admission and were available in Edinburgh from the SLTU database. The clinical details, including patient's history and biochemistry results were sought from the clinical notes in the referring hospital and SLTU. Data collected included plasma paracetamol concentration at initial presentation and the timing of this following overdose, the presence of risk factors for enhanced hepatotoxicity, use and timing of NAC treatment and liver function tests. Patients with a plasma paracetamol concentration below threshold were identified and reviewed. Information on the overall pattern of paracetamol poisoning was obtained from a survey of hospitals in North East England performed in 1994 [278] , and from review of patients with paracetamol poisoning presenting to the Newcastle Hospital NHS Trust during 2004. Data from the SLTU in Edinburgh was collected by myself. The data collection for Newcastle, risk analysis and cost-benefit calculations were performed by colleagues in Newcastle. The results presented in this chapter are a summary of the combined data sets.

4-3: Results

During the period of study, 696 patients (522 SLTU and 174 Newcastle) with possible paracetamol hepatotoxicity were admitted to the two liver units. Of these, 553 (79%) presented more than 15 h post-ingestion and in 19 (2.7%)

there was no adequate information available. Of the remaining 124 presenting within 15 h, 105 (81%) had a plasma paracetamol above the appropriate treatment line, and 19 below it. Of these 19, 5 cases were excluded; in two cases because plasma paracetamol had been taken less than 4 h after ingestion and results were therefore uninterpretable, and in three cases liver function tests or clotting factor was already deranged at presentation, indicating the paracetamol overdose may have been taken earlier than stated (Figure 4.1).

Thus 14 patients (6 from SLTU), 10 female and 4 male, with mean age (SD) of 30.4 ± 10.8 y were admitted to a liver unit after presenting within 15 h of overdose, with no evidence of abnormal liver function, and with a plasma paracetamol concentration below the appropriate treatment line (Figure 4.1) at presentation (for raw data for cases from SLTU see appendix 4.1).

Eight of these patients had normal venous bicarbonate concentrations at initial presentation; results were not available in the other six. Ten had no recorded features to indicate high risk; of these, four were below the “100 line”, four between “100 and150 lines” and two between the “150 and 200 lines”. Four patients were at high risk, all as a result of excess alcohol consumption, and all had paracetamol concentration below the “100 line”.

Two patients were treated with NAC soon after presentation, but the remaining 12 were not treated until abnormal liver function or clotting

developed. Two patients died; one after undergoing liver transplantation, and other from sepsis. The remainder recovered.

Figure 4.1: Patient inclusion and exclusion diagram

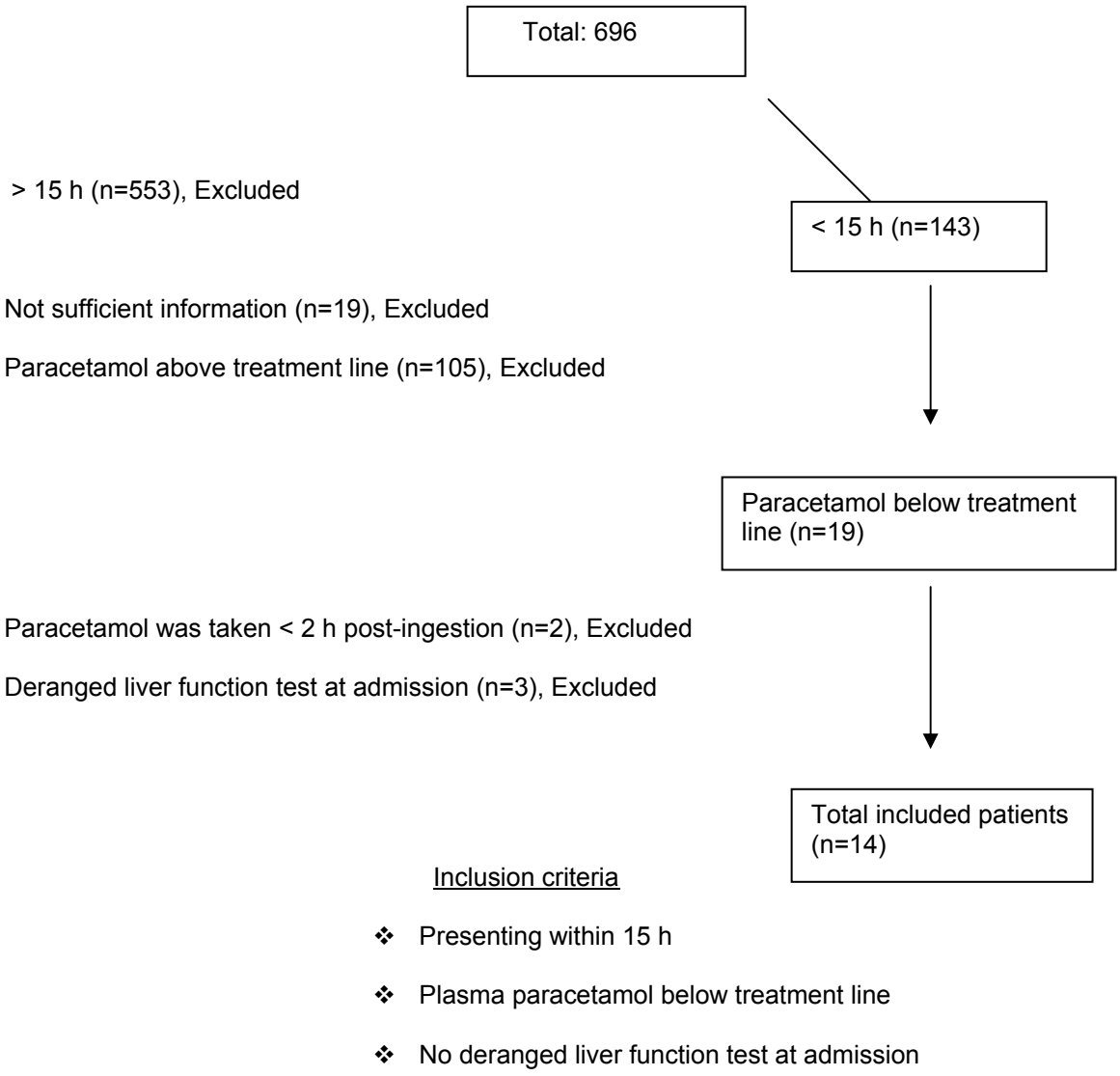


Table 4.1 : Demographic and characteristic of patients with paracetamol overdose presenting within 15 h post-ingestion with normal liver function and plasma paracetamol concentration below current UK guideline (n=14) to two liver centres (SLTU and Newcastle liver centre).

SLTU: Scottish Liver Transplant Unit, P'mol: paracetamol; OD: overdose; M: male; F: female; Max: maximum; TP: transplantation; HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; AC: acetylcysteine; INR: international normalized ratio; PT: prothrombin time; NK: not known; Outcome: R: recovered and D: Died

Patient number (case number and code in SLTU)	Age and Sex	P'mol dose (g)	P'mol level (mg/l)	Interval between OD and sample (h)	Relationship To treatment line	Co-ingestion	Relevant conditions	Risk Status	Interval from OD to NAC infusion (h)	Max INR/PT	Time from OD to max INR (h)	Max ALT (IU/l)	Time from OD to max INR (h)	Liver TP	Outcome
1 (SLTU) (314, MM080409)	40/F	25	45.6	6.0	Below 100	Alcohol	Hysterectomy for cancer 10 years earlier	Normal	30	INR 3.1	63	3345	72	No	R
2 (SLTU) (260, SL050351)	21/F	10	16.6	14.0	Below 100	Ecstasy, alcohol (previous day)	Cardiac failure, chronic alcohol excess	High	30	INR 11.3	56	9740	48	No	R
3 (SLTU) (432, CR070556)	40/F	29	62.5	6.0	Below 100	Codeine, fluoxetine, diazepam	-	Normal	16	INR 9.1	20	10183	84	No	R
4 (SLTU) (11, DA030015)	26/F	10	95.2	6.0	100-150	Alcohol, salicylates	-	Normal	Not treated	INR 3.2	80	11000	57	No	R
5 (SLTU) (75, SC060100)	29/F	48	18.1	15.0	100-150	Codeine, paroxetine	HAV, HCV, HIV ,antibodies, cardiac failure	NK	18	INR 4.8	55	9945	63	No	R
6 (SLTU) (169, NG040228)	29/F	10	93	5.0	Below 100	-	Cardiac failure	Normal	48	INR 11.8	51	7430	65	No	R
7 (Newcastle)	NK/F	NK	24.5	4.2	Below 100	Alcohol	Chronic alcohol excess	High	8	INR 10.9	53	13173	40	No	R
8 (Newcastle)	26/M	17.5	84	4.0	Below 100	Benzodiazepine, codeine, ecstasy	Possible p'mol OD one day earlier	Normal	26	PT 87 s	61	-	-	No	R
9 (Newcastle)	30/F	13	71	8.3	150-200	-	-	Normal	32	PT 82 s	81	9380	48	No	R
10 (Newcastle)	55/M	15	61	5.7	Below 100	Alcohol, benzodiazepine	Chronic alcohol excess	High	47	Pt 64 s	NK	4780	50	No	R
11 (Newcastle)	17/F	25	136	4.0	100-150	-	-	Normal	24	PT 76 s	58	4610	96	No	R
12 (Newcastle)	38/M	10	56	4.0	Below 100	Salicylate, ibuprofen	Chronic alcohol	High	NK	PT 35 s	90	-	-	No	D
13 (Newcastle)	15/F	7.5	170	4.0	150-200	Alcohol	-	Normal	33	PT 160	52	11396	46	Yes	D
14 (Newcastle)	29/M	24	107	4.0	100-150	Alcohol	-	Normal	24	PT 79 s	42	114900	52	No	R

In data collected from patients presenting with paracetamol overdose (n=352) to the Newcastle Clinical Toxicology Service in 2004, 71% (250) had plasma paracetamol under the “100 line”, 15% (53) between “100 and 150 lines” and 3.8% (13) between “150 and 200 lines”. This figure was similar to data collected from six A&E departments in the north-east of England in 1994 (n=287). The proportions of all patients presenting with plasma paracetamol concentrations at presentation below “100 line", between “100 and 150 lines “and between “150 and 200 lines” was 64% (184), 13% (37) and 6.4% (18), respectively [278].

4-4: Discussion

These data confirm the previous observation [218] that some patients with relatively low plasma paracetamol concentrations and normal liver function tests and clotting factors at admission when apparently presenting within 15 h of overdose develop severe, and occasionally fatal, hepatic necrosis. In the current systematic retrospective analysis, about 2% (14/696) of patients admitted to liver units following paracetamol overdose fell into this category.

From the catchment populations of the liver units concerned and the time periods studied, (95 million person-years population) this equates to a presentation rate of 0.15 episodes per million populations per annum [(14/95,000,000) *1000,000] or about nine UK case annually [(60,000,000*0.15/1000,000)].

In the context of the frequency of paracetamol overdose, these cases therefore occur very infrequently. The possibility that, in some of these cases, unexpected hepatotoxicity developed because the interval between overdose and presentation was not given or recorded accurately cannot be excluded. In addition some patients with liver failure may not have been referred for assessment.

The previous study [278;279] reported an annual presentation rate for paracetamol overdose of 750 cases/million population/year. Assuming the same presentation rate, the total number of patient presenting with paracetamol overdose during the study population is 71250 (750*95). If the number of patients presenting in each concentration range was assumed as midway between the figures obtained in 1994 [278] and 2004 (67.5% below “100 line”, 14% between “100-150 lines” and 5.1% between “150-200 lines), the numbers of patients presenting in each paracetamol concentration range each year can be derived (48093 below “100 line”, 9975 between “100-150 lines” and 3634 between “150-200 lines”). Using data provided by this study on the numbers of patients requiring liver unit admission in each of these concentration ranges (8 below “100 line”, 4 between “100-150 lines” and 2 between “150-200 lines”), it is possible to estimate the risk for each group. For patients with concentrations between the 150 and 200 lines, the 100 and 150 lines and below the 100 line, respectively, these risks would be approximately 1:1250, 1:1850 and 1:4400. However, these estimates should be interpreted with caution: proportions are based on limited patient

numbers, and the data collection periods and geographic areas are not identical with the liver unit data presented here. Furthermore, factors for enhanced hepatotoxicity are ignored, as there was inadequate information about presentation patterns in relation to them. The frequency of severe poisoning may have been reduced by legislation affecting pack sizes [284]. Not all patients with severe hepatotoxicity will be referred to a liver unit. Finally, an unknown number of patients in each category will have been treated with NAC in spite of their low initial paracetamol concentration, especially following the Bridger [218] publication. This may reduce the numbers of these patients needing liver unit admission, and thus result in an underestimation of risk. The proportion of patients treated with NAC increased from 25% to 76% for patients between the 150 and 200 lines, and from 2% to 15% for those between the 100 and 150 lines comparing the 1994 [278] and 2004 North-East England data sets. On the basis of these data, use of the 150 line for determining need for treatment would prevent only a few liver unit admissions; use of lower thresholds still would require treatment of very large patient numbers and would avoid only a few further episodes. These marginal benefits need to be offset against the inconvenience and costs of therapy and the risk of adverse reactions. Although usually not severe, anaphylactoid reactions to acetylcysteine appear more common in patients with lower plasma paracetamol concentrations [245]. In a randomized controlled trial, drug-related adverse effects occurred in 45% and anaphylactoid reactions in 18% of recipients of the standard acetylcysteine infusion schedule [285]. It is possible that lower

doses of acetylcysteine may be effective and safer for patients with paracetamol concentrations below current UK thresholds. Clinical trials of these would be helpful, but are difficult to perform because of the very large numbers of participants that would be required to achieve adequate study power to demonstrate efficacy in this group. Larger observational studies, which include the simultaneous collection of data on presentation patterns and risk factors, would be helpful in order to obtain more accurate estimates of risks without antidotal treatment in these patient groups. Abnormal liver function tests were present at presentation in some of the patients who went on to develop severe hepatic dysfunction, suggesting a longer interval between overdose and presentation than that suggested by the history. It may therefore be appropriate that liver function tests should be performed on all patients at their original presentation; those with abnormal values should receive acetylcysteine irrespective of the plasma paracetamol concentration unless an alternative cause can be demonstrated.

4-5: Conclusion

Only a very small percentage of patients with plasma concentrations below UK treatment threshold may develop features of liver toxicity. In the view of the rarity of this event, the costs of therapy and risk of adverse reactions the results of this study does not suggest a need to lower current UK thresholds for antidote therapy in paracetamol overdose.

Chapter V: The Mechanisms and the Associated Factors Involved in Anaphylactoid Reactions to Acetylcysteine in Patients with Paracetamol Overdose

5-1: Introduction

The current protocol for antidote therapy in paracetamol poisoning in the UK is the Prescott protocol [203], which is a step-down, 20-hour intravenous NAC infusion (150 mg /kg over 15 min in 200 ml 5% dextrose, followed by 50 mg/kg in 500 ml 5% dextrose over 4 hours and 100 mg/Kg in 1000 ml 5% dextrose over 16 hours). IV infusion of NAC causes adverse reactions in some patients [237]. The frequency of such reactions, varies from 3-9% [238-240] to 48.4% [241] in different studies. Some factors including asthma [244;245] and low paracetamol concentration [239;241;245;286] have been reported to associated with ADRs. Death has been report in an asthmatic patient due to adverse effects of a therapeutic dose of IV NAC [246]. In 1984, two deaths were reported due to ADRs to overdose of IV NAC [238]. In both these cases the dose of NAC given was 10 times higher than therapeutic. The high incidence of ADRs to IV NAC (50%) in healthy individuals not receiving paracetamol is further evidence that paracetamol itself may have some protective effect against ADRs to NAC [231].

The mechanisms of ADRs to NAC remain unclear. A non-allergic release of histamine has been suggested as a potential mechanism of ADRs [247]. An in vitro study has shown histamine release induced by NAC [248]. Previous studies on acute allergic reactions, and anaphylactic shock, in other situations have shown an increase in plasma concentrations of mast cell products (histamine and tryptase) [249-252], endothelial injury parameters (von

Willebrand factor [vWf]) and fibrinolytic parameters (tissue plasminogen activator [tPA]) [251]. Healthy volunteers given therapeutic doses of NAC intravenously who developed ADRs had elevated factor VIII and vWf within an hour of starting NAC. The authors suggested that NAC induces release of vWf from endothelial cells in subjects who develop adverse effects [231].

Interleukin 6 (IL6), released from mast cells and basophils, has also been reported to contribute in allergic reactions [253]. IL6 also stimulates C-reactive protein (CRP) production and the two correlate with one another in acute allergic reactions [257].

The aim of this study was to examine the profile of ADRs to NAC and potential risk factors in a patient cohort with paracetamol overdose. In addition the potential mechanisms of ADR to NAC were also explored.

5-2: Method

This was a prospective study on patients admitted to the Royal Infirmary of Edinburgh from July 2006 to May 2007 with paracetamol overdose who required NAC treatment. The study was approved by the Local Ethics Committee and informed consent form (see appendix 5.1, 5.2 and 5.3) was obtained from all patients who took part. All patients who received antidotal therapy were carefully monitored for adverse effects. Patients were seen during their hospital stay, with

case note review and telephone follow up of patients discharged from hospital over night, at weekends or public holidays. Data collected included age and gender; type and number of paracetamol tablets taken; time(s) and date of ingestion; plasma paracetamol concentration at admission; UK risk categorisation for treatment [31]**;** alcohol history; history of allergy, including atopy, asthma or drug; family history of allergy; previous NAC treatment; history of ADRs to NAC; nature of any reaction to NAC in the current admission, together with treatments given, including necessity to interrupt the NAC infusion (see appendix 5.4, 5.5 and 5.6).

In a subset "convenience" sample, a more intense study was conducted in patients who gave additional consent. This more detailed study involved blood sample collection immediately before and during antidote treatment. Measurements included (see also appendix 5.7):

-Paracetamol: baseline and 4h after NAC

-Histamine: baseline, 15min, 30min, 1h, 2h

- NAC: baseline, 30min, 2h, 4h, 20h

- Tryptase: baseline, 30min, 1h, 2h

-IL6: baseline, 30 min, 1h, 2h, 4h, 20h

-C-reactive protein (CRP): baseline, 1h, 2h, 4h

-Clotting factors (II, V, VII, VIII, IX, X, XI, XII): baseline, 30min, 1h, 2h, 4h, 20h

-vWf: baseline, 30min, 1h, 2h, 4h, 20h

The blood was collected from the contra-lateral arm to that in which the NAC infusion was given. In addition, systolic blood pressure (SBP), diastolic blood pressure (DBP), temperature (T), O_2 saturation (O2 Sat) and peak expiratory flow rate (PEFR) were measured at baseline, 30 min, 1h, 2h, 4h and 20h after NAC infusion initiation. The precise details of any reactions, including time of initiation, any treatment and termination, were recorded. Hypotension was defined as a SBP <90 mmHg. Tachycardia was defined as pulse rate>100 and fever as temperature ≥ 38 ºC.

In view of the sampling protocol, this study was carried out in daylight hours.
In both parts of the study, overall severity of reaction was graded clinically as minimal if patients had no reaction or only gastrointestinal (GI) signs and symptoms with or without anti-emetic treatment; moderate if patients had GI signs and symptoms requiring temporary NAC infusion cessation and/or mild flushing, pruritus and/or breathlessness (in the intensive study reduction in PEFR ≥ 25 and <50 % from baseline), and/or mild chest pain; and severe If NAC was stopped for adverse effects such as severe flushing and/or respiratory distress (in the intensive study: ≥ 50% reduction in PEFR from baseline) and/or severe chest pain.

To examine the stability of histamine in plasma if processed at different time points after blood collection an experiment was conducted on 8 healthy volunteers. 4 male and 4 female subjects, older than 16 year-old and non-

pregnant, took part in the study. In this group plasma histamine of samples collected at once but spun at different time points after collection were compared.

5-2-1: Blood collection, sample processing and laboratory analysis

Two cannulas were inserted, one in each arm: one for NAC infusion and one, in the contra lateral arm for blood collection. After inserting the sampling cannula 5 ml normal saline was flushed into the vein. Before blood sampling at each time point 5 ml blood was collected and discarded. After blood sampling at each time point 5 ml normal saline was flushed. More details of blood collection, sampling process and laboratory analysis for each marker is as shown below. Plasma histamine analysis was measured by myself and a laboratory technician in Clinical Pharmacology Unit in the University of Edinburgh. Measurement of plasma NAC was performed by the Free radical Research Facility, UHI Millennium Institute, Inverness (Prof Megson). The rest of tests were performed by biochemistry and haematology technicians in the Royal Infirmary of Edinburgh clinical laboratories.

5-2-1-1: Plasma histamine

3 ml of blood was collected by venepuncture with 5 ml syringe and immediately transferred to two aliquots (1.5 ml each, containing EDTA) and after shaking on a roller (5 min), it was cooled in crushed ice and spun by a micro centrifuge

(15000 rpm, 3 minutes, 4ºC) within 30 minutes. The supernatant was transferred into two plane aliquots and stored in -80ºC for later analysis.

In the histamine experiment study, 15 ml blood was collected (using 10 ml and a 5 ml syringe) at once. The blood was immediately distributed in 4 paired aliquots, 1.5 ml each. Samples were shaken on the roller for 5 minutes and cooled in crushed ice immediately. Each paired sample was spun at 5min, at 20min, 35min and 65min after collection. The supernatant was transferred into two plain tubes and stored at -80 ºC and analysed within 2 months. Plasma histamine was measured using an EIA (Enzyme Immunoassay) kit manufactured by Bio Source Europe S.A. The sensitivity of the technique was 0.1ng/ml for plasma histamine.

5-2-1-2: Plasma NAC

The blood collection and sampling process was the same as histamine. NAC was measured by high performance liquid chromatography (HPLC; Agilent 1200 series with fluorescence detector, Agilent Technologies, South Queensferry, UK) using a published method for thiol analysis [287-289] with minor modifications.

5-2-1-3: Plasma tryptase

10 ml blood was collected by venepunture by a plain white top tube, allowed for 10-15 min to clot in room temperature. The sample was spun (3000 rpm, 4 ºC,

15 min) within 30min and the supernatant was stored in two aliquots in -80ºC for later analysis. Plasma tryptase was measured by a fluoroenzyme immunoassay (ImmunoCAP Tryptase; Phadia AB, Uppsala, Sweden), which detects both α- and β-tryptase (mean: 3.8 µg/l, 95% upper limit: 11.4 µg/l, detection limit <0.1 µg/l).

5-2-1-4: Plasma tPA activity and antigen

5 ml blood was taken by 5ml syringe and transferred immediately to Stabilyte tube. The sample was shaken on roller for 5min and cooled in crushed ice and spun (3000 rpm, 15 minutes, 4ºC) within 30 min. The supernatant was stored in -80ºC in two plain aliquots. The plasma tPA activity and antigen were assayed by ELISA (tPA Combi Actibind, Technoclone, Vienna, Austria).

5-2-1-5: Clotting factors, vWf and IL6

9 ml blood was collected by venepunture (using three 3ml green top tubes). The samples were shaken for 5 min on a roller, cooled in crushed ice and spun (15000 rpm, 15 minutes, 4ºC) within 30 min and stored in two plain aliquots in -80ºC. The plasma clotting factor activity assays were all performed by ELIZA using the CA 600 instrument manufactured by Sysmex. Plasma vWf antigen was performed by an ELISA (Enzyme-Linked Immuno Sorbent Assay) technique using antibodies supplied by Dacko, Denmark. Plasma IL6 was measured by ELISA (Quantikin Human IL-6, R&D Systems, USA).

5-2-1-6: Plasma paracetamol and salicylate

5 ml venous blood was collected by venepunture using (5 ml orange top tube) and shaken on a roller for 5 min. The sample was cooled in crushed ice and spun (15000 rpm, 15 min, 4ºC) within 30 min. The supernatant was stored in two aliquots in -80ºC for later analysis. Plasma paracetamol was measured by an aryl acyl amidase enzymic method (Ortho Clinical Diagnostics, UK) on a Vitros auto-analyser.

5-2-1-7: CRP

5 ml blood was taken by venepunture using (orange top tube). After shaking on a roller for 5 minutes it was cooled in crushed ice and spun within 30 minutes (3000 rpm, 4 ºC, 15 min). Supernatant was extracted and stored into two plain aliquots in -80ºC for later analysis. Plasma CRP was measured by an immunoturbidometric technique.

5-2-2: Measurement of PEFR

PEFR (peak expiratory flow rate) is the patient's maximum ability to expel air from the respiratory system. It is measured by a small hand-held device called a peak flow meter. Peak flow is a measure of the degree of restriction in the airways by measuring airflow rate. Peak flow reading is high when patients are

well and is lower when there is bronchoconstriction. The peak flow meter is normally used to monitor severity and treatment options in asthmatic patients [290]. The main weakness of peak flow meter is that it is patient dependent, and if patients do not co-operate may not be an accurate reflection of airway function. Its advantages are its simplicity in use, and general reproducibility in co-operative patients.

5-2-2-1: Method of measurement of PEFR

Step 1: make sure that marker or arrow on the Peak Flow Meter was at the bottom of the numbered scale (zero or the lowest number on the scale).

Step 2**:** patients were asked to remove gum or any food from their mouth, to take a deep breath (as deep as they could) and to put the mouthpiece of the peak flow meter into their mouth. They were told to close their lips tightly around the mouthpiece, made sure to keep their tongue away from the mouthpiece and in one breath blow out as hard and as quickly as possible until they emptied out nearly all of the air from their lungs.

Step 3: the force of the air coming out of the respiratory system caused the marker to move along the numbered scale. The number was recorded as peak flow.

Step 4**:** the same steps were repeated twice and the highest number was recorded [290].

5-2-2-2: Severity of bronchospasm according to PEFR

Less than 25% reduction in PEFR from baseline was considered as no or mild, ≥25% and <50% reduction in baseline PEFR: moderate, and ≥50% reduction was considered as severe bronchospasm [290].

5-3: Statistical analysis

Analysis in the total cohort focused on the pattern of adverse effects and potential risk factors. In the more intensive study the relationship between severity of ADRs and the changes in the various biological markers were examined. Data are presented as mean and 95% confidence intervals or median and interquartile range. For two-group comparisons, the Mann-Whitney U test was used and for multiple group comparisons of continuous data, a Kruskal-Wallis H test was performed. AUC (area under the curve) analyses of the change from baseline histamine concentration was undertaken between 0 and 120 min, and a simple linear imputation method was used to minimize the potential effects of missing data on AUC analyses. A Chi-square tests was performed to compare categorical data. Univariate analyses were performed using Spearman's rank correlation, and possible risk factors were examined using binary logistic regression (stepwise backward) with exclusion of factors if $p > 0.1$.

5-4: Results

5-4-1: Result of total cohort

5-4-1-1: Demographic data

Over the period of the study, 193 patients were admitted to the Toxicology unit of Royal Infirmary of Edinburgh who required IV NAC infusion following paracetamol overdose. Data were not available in 24 cases because the patients had absconded from the ward or took their own discharge against medical advice and could not be interviewed. Therefore, the study population consisted of 169 patients (71 men, 42.0%) with mean (95% confidence interval) age 37 y (35 to 39 y).

5-4-1-2: Clinical features of ADRs

Reported adverse effects were nausea (70.4%), vomiting (60.4%), flushing (24.9%), pruritus (20.1%), dyspnoea (13.6%), chest pain (7.1%), dizziness (7.7%), fever (4.7%), wheezing and bronchospasm (7.1%), and rash and urticaria (3.6%) (Table5.1).

None of the patients developed hypotension. Severity was graded minimal in 101 (39: no ADRs, 62 mild ADRs), moderate in 51, and severe in 17 patients (Figure 5.1 and Table 5.2). NAC infusion was stopped temporarily due to adverse effects in 18 patients.

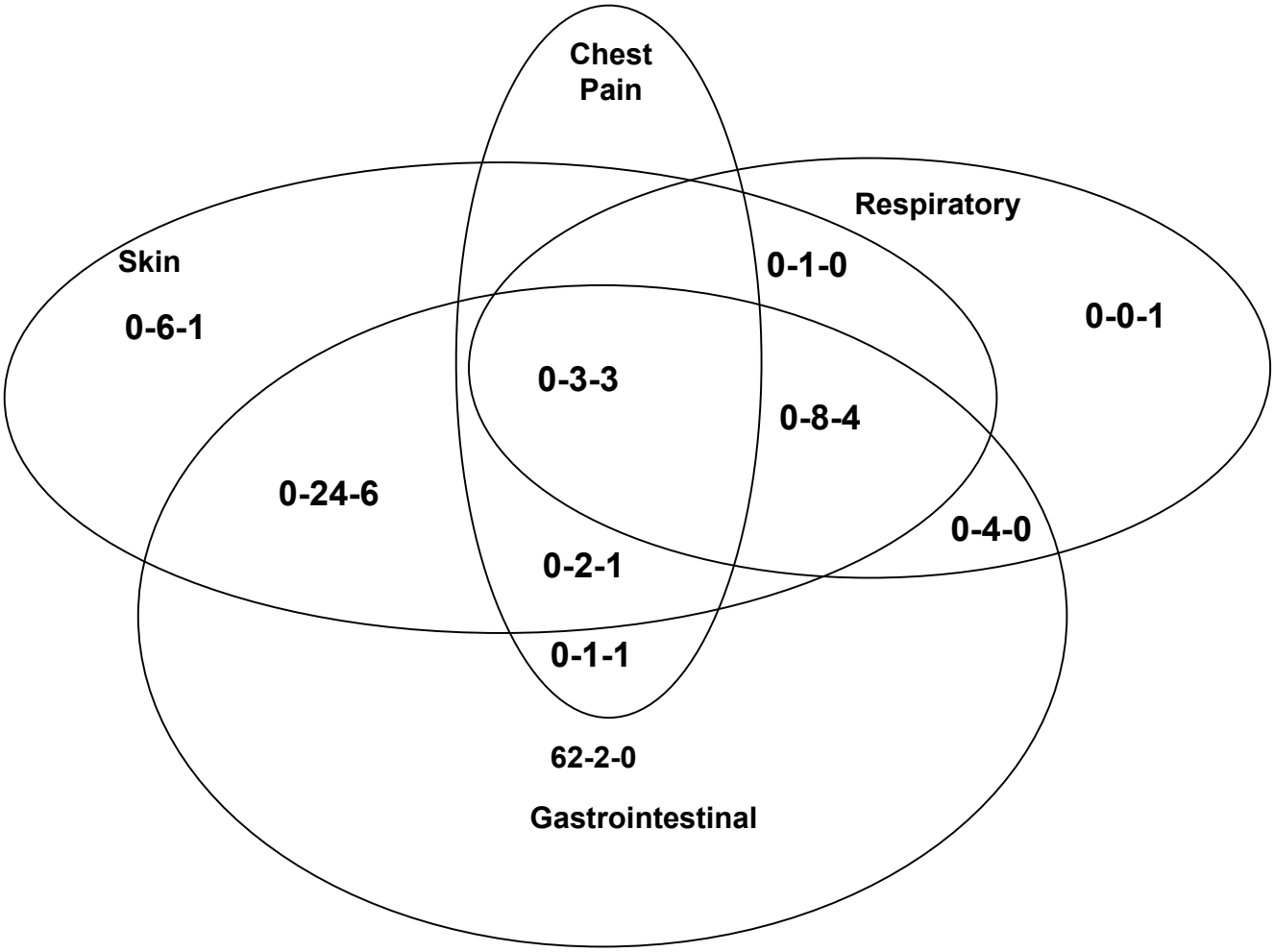
Table 5.1: Occurrence of ADRs to intravenous NAC in patients with paracetamol overdose (n=169).

Signs & Symptoms		**n (%)**
Gastrointestinal	Nausea	119 (70.4%)
	Vomiting	102 (60.4%)
	Abdominal discomfort	8 (4.7%)
Skin	Flushing	42 (24.9%)
	Pruritus	34 (20.1%)
	Rash and urticaria	6 (3.6%)
Respiratory	Dyspnoea	23 (13.6%)
	Wheeze & bronchospasm	12 (7.1 %)
	Coughing	4 (2.4%)
Other	Dizziness	13 (7.7%)
	Chest Pain	12 (7.1%)
	Fever (temperature ≥38 ºC)	8 (4.7%)
	Hypotension	0 (0.0%)

Table 5.2: History of asthma, drug allergy, family history of allergy and previous ADRs to NAC in the group with minimal and moderate or severe ADRs to NAC.
M: male, F: female.

Severity of ADRs	**Minimal** (no:39, mild: 62)	**Moderate and severe** (moderate: 51, severe: 17)
Total number (n=169)	101	68
Gender (M/F)	39/62	32/36
Age (mean 95% CI) (y)	38.1 (35.0-41.2)	34.8 (31.6-38.0)
Paracetamol level at admission (mg/l) (mean 95% CI)	130.0 (114.6-145.3)	104.4 (81.2-127.7)
Asthma, n (Yes/No)	13/88	10/58
Drug allergy, n (Yes/No)	17/84	17/51
Family allergy, (Yes/No) Total=151, unknown=18	32/59	32/28
Previous allergy to NAC, (Yes/No) Total: 52, Unknown: 19, No previous treatment with NAC: 98	23/10	15/4

Figure 5.1: Diagrammatic representation of adverse effect profiles in patients treated with acetylcysteine for paracetamol poisoning, categorised by adverse effect severity: minimal-moderate-severe (n= 169, including 39 patients with no adverse effects).



5-4-1-3: Paracetamol

Plasma paracetamol concentration was lower in patients with severe adverse effects [median (IQR) in severe: 46 mg/l (0 to 101 mg/l), moderate: 108 mg/l (54 to 178 mg/l) and minimal: 119 mg/l (77 to 174 mg/l)], p=0.002 by 3-way comparison. Concentrations were undetectable in 4 patients; two had taken a staggered overdose, and two had presented late (at 21h and at 48h after ingestion).

5-4-1-4: Associated factors of ADRs

Logistic regression (stepwise backward) analyses of possible risk factors of ADRs showed that moderate to severe adverse effects were correlated inversely with plasma paracetamol concentration [odds ratio (95% CI): 0.99 (0.99 -1.00)] and male gender [odds ratio (95% CI): 0.45 (0.22 - 0.92)], and correlated positively with a family history of allergy [odds ratio (95% CI): 2.89 (1.39-5.99)]. No significant correlations were found with age, history of asthma, or previous drug allergy (Table 5.2 and 5.3).

Table 5.3: Stepwise backward binary logistic regression for possible variables associated with moderate to severe adverse effects of NAC.

* Change in risk related to each year of life and each mg/l increase in paracetamol concentration, other variables treated as categorical data. Analyses were made between two groups: minima ADRs group (n=101) and moderate or severe ADRs (n=68).

	Odds ratio (95% CI)	**p-value**
Univariate analyses		
Male gender	0.40 (0.19 to 0.84)	0.016
Age (y) *	0.98 (0.95 to 1.00)	0.102
[paracetamol] (mg/l) *	1.00 (0.99 to 1.00)	0.062
Asthma	1.09 (0.42 to 2.83)	0.867
Drug allergy	1.82 (0.73 to 4.52)	0.200
Family history of allergy	2.36 (1.09 to 5.08)	0.029
Constant	6.02	0.032
Logistic Stepwise backward regression analyses		
Male gender	0.45 (0.22 to 0.92)	0.028
[paracetamol] (mg/l) *	0.99 (0.99 to 1.00)	0.043
Family history of allergy	2.89 (1.39 to 5.99)	0.004
Constant	2.452	0.147

5-4-2: Result of the intensive study

5-4-2-1: Demographic data

22 patients (11 male and 11 female) with mean age (95% CI) of 34.6 (21-45) y were recruited into the more intensive study. These patients were almost all studied in daylight hours and therefore are not representative of the total cohort with respect to nature of paracetamol overdose, often being later presentations.

Some patients did not complete the whole course of the study because they did not require a full course of NAC treatment, self-discharged or withdrew from the study. All patients completed the first 2 hours of the study, 18 the first 4h and 16 completed the full study (20h).

5-4-2-2: Severity of ADRs

10 subjects (45%) had minimal, 5 (23%) moderate and 7 (32%) severe ADRs (Table 5.4 and 5.5).There was no significant difference between groups with respect to systolic blood pressure at baseline or during antidote infusion (Table 5.6). The onset of ADRs in most subjects occurred within the first hour and 15 min after commencement of treatment (see appendix 5.8). There was no significant difference between these groups in terms of age and gender.

5-4-2-3: Plasma Paracetamol

As in the total study paracetamol at baseline (median and IQR) was significantly lower in patients with severe ADRs (severe: 0.0 mg/l [0.0-41.0] vs. minimal: 137.8 mg/l [59.5-230.0]; p=0.02.

5-4-2-4: Plasma NAC

As expected, plasma NAC concentration was maximal at the 30min time point after infusion. There was no difference in plasma NAC in the groups with different ADRs severity at any time point (Table 5.7) (see appendix 5.9 for raw data).

Table 5.4: Clinical features of ADRs to NAC in patients with severe ADRs, n=7 (intensive study)

Features of ADRs	**Case 1**	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**	**Case 7**
Rash (Yes, No)	No	No	No	No	No		No
Pruritus (Yes, No)	No	No	Yes	No	No	Yes	No
Urticaria (Yes, No)	No	No	No	No	No	No	No
Angioedema (Yes, No)	No	No	No	No	No	No	No
Nausea(Yes, No)	Yes	No	Yes	Yes	Yes	Yes	No
Vomiting (Yes *, No)	Yes (Moderate)	No	Yes (Moderate)	Yes (Moderate)	Yes (Severe)	Yes (Moderate)	No
Chest Pain (Yes, No)	No	No	No	No	No	No	No
Abdominal cramp (Yes, No)	No	No	No	No	No	No	No
Diarrhoea (Yes, No)	No	No	No	No	No	No	No
Flushing (Yes, No)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Fever (Yes, No)	No	Yes	No	No	No	No	No
Coughing (Yes, No)	No	Yes	Yes	No	Yes	No	Yes
Wheezing (Yes, No)	No	Yes	No	No	No	No	No
Dyspnoea (Yes, No)	Yes	Yes	Yes	No	Yes	No	Yes
Bronchospasm (Yes **, No)	Yes (Moderate)	Yes (Severe)	No	No	Yes (Severe)	No	Yes (Moderate)
Chest Pain (Yes***, No)	No	No	Yes (Moderate)	No	Yes (Severe)	No	Yes (Moderate)
Tachycardia (Yes, No)	No	Yes	No	No	Yes	No	No
Hypertension (Yes, No)	No	Yes	No	No	Yes	No	No
Hypotension (Yes, No)	No	No	No	No	No	No	No
Faint/dizziness (Yes, No)	No	Yes	No	No	No	No	No

* Vomiting: mild: no treatment required; moderate: treatment required; severe: required temporary IV NAC infusion stop

** Bronchospasm: moderate: if reduction in baseline PEFR ≥25% and ≤50%; severe: if reduction in baseline PEFR≥50%

*** Chest Pain: moderate: feeling tight chest with no sharp pain; severe: with a sharp pain in the chest requiring temporary stop in NAC infusion

Table 5.5: Peak flow rate (L/per min) at base line and time points (30min, 1h, 2h, 4h and 20h) after IV NAC commencement. ND: No data available.

Pt No	Severity	PEFR BASE L/pm	T1 h	PEFR 1	T2	PEFR 2	T3	PEFR 3	T4	PEFR 4	T5	PEFR 5
5	1	ND		ND		ND		ND		ND		ND
6	1	400.00		ND	0.90	470.00	2.10	470.00	4.00	420.00	20.00	520.00
7	1	340.00	0.50	250.00	1.30	380.00	2.30	220.00	4.50	250.00	20.50	340.00
9	1	ND		ND		ND		ND		ND		ND
13	1	ND		ND		ND		ND		ND		ND
17	1	600.00	0.50	550.00	1.00	575.00	2.10	430.00	4.10	440.00	22.00	520.00
18	1	360.00	0.50	300.00	1.00	300.00	2.00	340.00	5.00	340.00	21.00	370.00
19	1	575.00	0.60	420.00	1.10	390.00	2.10	430.00	4.10	420.00	20.50	440.00
20	1	180.00	0.50	150.00		ND	2.00	150.00	4.00	150.00	20.00	200.00
22	1	280.00	0.50	230.00	1.00	210.00	2.30	230.00	4.00	200.00		ND
1	2	500.00	0.50	480.00	1.00	450.00	2.00	490.00	4.50	500.00		ND
2	2	490.00	0.50	450.00	1.10	450.00	2.20	440.00	4.50	ND	20.00	450.00
12	2	210.00		ND	1.10	200.00	2.10	220.00	4.60	180.00	20.20	240.00
15	2	ND		ND		ND		ND		ND		ND
21	2	350.00	0.50	410.00	1.00	400.00	2.10	400.00	4.20	400.00	20.00	350.00
3	3	480.00	0.50	300.00		ND	3.00	440.00	4.00	370.00	20.30	410.00
4	3	340.00	0.50	120.00	1.00	290.00	2.00	340.00		ND		ND
8	3	260.00	0.40	390.00	1.50	250.00	2.50	300.00	4.10	320.00	20.50	340.00
10	3	520.00		ND		ND				ND		ND
11	3	600.00	0.60	250.00	1.30	440.00	2.10	500.00	4.00	600.00	20.30	570.00
14	3	380.00	0.50	330.00	1.00	300.00	2.40	350.00		ND		ND
16	3	300.00			1.00	200.00	2.00	270.00	4.20	300.00		ND

Table 5.6: Systolic blood pressure (SBP) at baseline and time points after IV NAC infusion commencement in the groups according to the severity of ADRs.

There was no significant difference in SBP between groups at baseline and any time points after IV NAC infusion commencement. n: number of subjects (intensive study).

SBP in the groups according to ADRs	Minimal Median and IQR, n	Moderate Median and IQR, n	Severe Median and IQR, n
baseline	127.0 (107.3-146.3), 10	112.0 (109.0-115.5), 5	123.0 (112.0-147.0), 7
30min	128.5 (105.5-154.5), 8	122.0 (117.0-127.0), 4	131.0 (125.0-171.5), 5
1h	128.0 (112.3-133.5), 10	116.0 (109.0-131.0), 5	146.0 (121.0-172.0), 6
2h	124.5 (106.8-155.5),10	117.0 (115.5-124.5), 5	125.0 (109.5-157.5), 6
4h	151.0 (113.0-168.8),10	128.0 (112.5-146.5), 5	133.0 (114.8-173.8), 4
20h	126.0 (114.0-140.5), 9	112.0 (109.50-127.3), 4	137.0 (97.0,-), 3

5-4-2-5: Plasma Histamine

There was no significant difference in plasma histamine concentrations between groups at baseline. After commencement of NAC, plasma histamine increased in the groups with moderate and severe ADRs and it reached maximum (2.5 fold increase) between 30 to 70 min. There was significant difference in change in plasma histamine between groups at 1h (p=0.02) (Figure 5.2) (see appendix 5.10, 5.11 and 5.12 for raw data).

The AUC of histamine-time expressed as change from baseline (median and IQR) was significantly different between groups (p=0.01):minimal: -6.4 ng/ml.min [-60.3-10.8]; moderate 25.6 ng/ml.min [2.9-128.7]; severe 49.0 ng/ml.min [21.0-

68.0].The significance level was between minimal and severe ADRS groups (p=0.005). The difference between AUC change of minimal and moderate group just failed to pass conventional significance level (p=0.06), perhaps due to small number of subjects in each group.

In the experimental study on 8 healthy volunteers there was no significant difference in plasma histamine concentration when centrifuged and separated either at 5min, 15min, 30min or 1h after blood collection (Table 5.8) (see appendix 5.13 for raw data).

5-4-2-6: Plasma tryptase

There was no significant difference in change in plasma tryptase concentration between groups at 30 min and 1h following IV NAC infusion. Plasma tryptase change at 2h was significantly different between groups, but not related to the severity of adverse reactions (Table 5.9) (see appendix 5.14 for raw data). Change in AUC tryptase (0-2h) was not significantly different between groups (p=0.22).

Median and IQR of AUC change of tryptase (0-2h) was -85.0 [-182.50- (-32.5)] µg/l.min in the minimal ADRs group; 59.50 [-254.35-207.50] in the moderate group and -67.0 [-106.0-81.0)] in the severe group.

Table 5.7: Median plasma NAC concentration (IQR) (mg/l) after intravenous infusion according to the severity of adverse effects: minimal, moderate, and severe.

NAC reached maximum concentration at 30min time point. After 30min NAC decreased steadily. There was no significant difference in plasma NAC concentration between groups with different ADR severities at any time point. n=number of subjects.

plasma NAC (mg/l) and time Median (IQR)	Minimal ADRs	Moderate ADRs	Severe ADRs
Baseline: 0.0	0.7 (-0.5-1.9) n=10	1.1 (-1.9-4.0) n=5	1.2 (-0.8-3.2) n=7
30min: 0.55 (0.52-0.58)	90.3 (72.6-108.1) n=10	89.5 (26.1-152.8) n=5	95.9 (64.4-127.4) n=6
2h: 2.06 (2.00-2.18)	47.6 (37.3-58.9) n=10	45.5 (31.0-59.9) n=5	34.5 (23.2-45.8) n=7
4h: 4.10 (4.0-4.30)	27.8 (17.7-38.0) n=10	36.3 (19.0-53.6) n=5	30.1 (20.7-39.5) n=4
20h: 20.08 (20.0-20.33)	15.6 (8.79-22.5) n=9	13.8 (-5.7-33.2) n=5	14.0 (-2.1-30.0) n=4

Figure 5.2: Median change in plasma histamine concentrations (ng/ml) at 15 min, 30 min, 1h and 2h after commencing intravenous NAC infusion from baseline according to the severity of ADRs: minimal (◆), moderate (■), and severe (▲).

Data in the table shows median and IQR and data in the graph represent median. 3 -group comparison showed a significant difference between groups at 1h time point (p=0.02). The difference was between groups with minimal and severe ADRs (p=0.01). n: number of subjects.

Change in plasma histamine (ng/ml) at time points Median (IQR)	Minimal ADRs	Moderate ADRs)	Severe ADRs
15min: 15.0 [15.0-18.0]	-0.25 [-0.64-(-0.03)]	-0.11[-0.16-1.13]	-0.05 [-0.21- 0.11]
30min: 33.0 [30.0-35.0]	-0.09 [-0.59-0.08]	0.33 [-0.11-1.23]	0.67 [-0.11-1.16]
60min: 65.0 [60.0-70.0]	-0.04 [-0.61-0.18]	0.50 [0.16-1.43]	0.63 [0.23-1.40]
120min: 124.0 [120.0-130.0]	-0.04 [-0.45-0.25]	0.02 [-0.2-0.82]	0.10 [0.16-0.31]

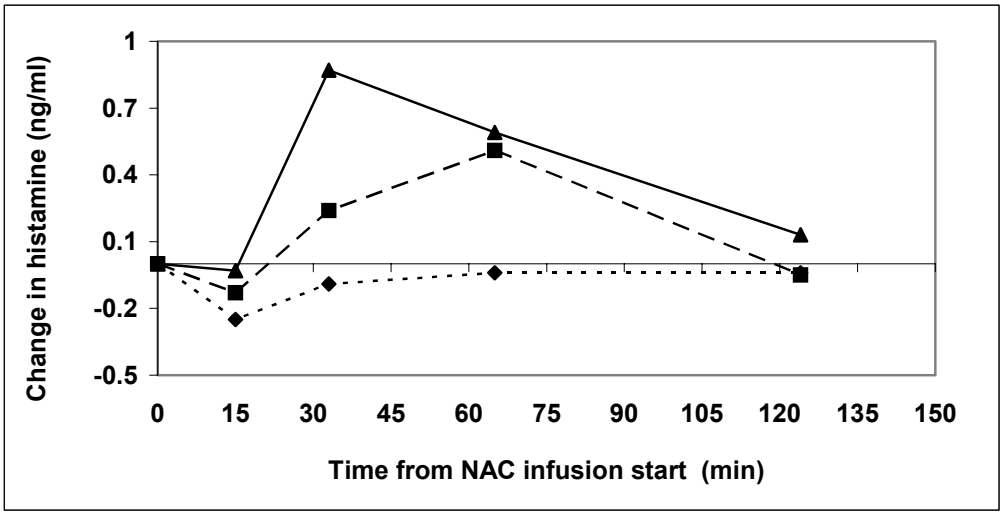


Table 5.8: Effect of delay in sample processing on plasma histamine assay (ng/ml) in 8 healthy volunteers (4 male and 4 female).

Samples were collected and cooled at once, but processed at different time points after blood collection (5min, 15min, 30min and 60min). Data are reported as median and IQR. There was no significant difference in plasma histamine when processed either at 5min, 15min, 30min or 1h after collection (p=0.939). n: number of subjects.

Time from collection to sample processing	Median and IQR (ng/ml)	n
5min	0.53 (0.48-0.82)	8
15min	0.62 (0.51-0.73)	8
30min	0.64 (0.35-0.78)	8
60min	0.55 (0.43-0.81)	8

Table 5.9: median change in plasma tryptase concentrations (µg/l) at 30 min, 1h and 2h after commencing IV NAC infusion from baseline according to the severity of ADRs (minimal, moderate and severe).

Change in plasma tryptase at 2h was significantly different between groups according to the severity (p=0.02) and the difference was between minimal and moderate ADRs (p=0.03) and minimal and severe ADRs (p=0.016). n=number of subjects

Change in plasma tryptase (µg/l) at time points after IV NAC infusion Median (IQR)	Minimal ADRs	Moderate ADRs	Severe ADRs
30min: 33.0 [30.0-35.0]	-1.16 [-1.37-(-0.18)] n=8	-0.18 [-1.82-(-0.02)] n=4	-0.89 [-1.54-0.82] n=6
60min: 65.0 [60.0-70.0]	-0.65 [-2.31-0.00] n=8	0.68 [-4.34-1.77] n=4	-0.67 [-1.27-0.42] n=7
120min: 124.0 [120.0-130.0]	-0.97 [-1.32-(1.14)] n=9	1.16 [-0.30-4.34] n=4	0.67 [-0.31-1.74] n=7

5-4-2-7: Plasma CRP and IL6

There was no significant difference in plasma CRP or plasma IL-6 between groups with different severity at baseline, or subsequently (see appendix 6.15 and 6.16 for raw data).

5-4-2-8: tPA antigen and activity

There was no significant change in plasma tPA antigen between groups with different severity at baseline or time points after NAC infusion. Change in plasma tPA activity at 1h and 2h were significantly higher in the severe group compared to minimal group (p=0.007 and p=0.02, respectively) (Table 5.10), however, AUC change of tPA (0-4h) was not significantly different between groups. Median and IQR of AUC change of tPA (0-4h) was -2.3 [-36.1-5.1] (u/ml.min) in the minimal group; 0.0 [-26.4-34.5] in the moderate and -10.9 [-49.8-76.6] in the severe group (see appendix 6.17 and 6.18 for raw data).

Table 5.10: Change from baseline in plasma tPA activity concentration (u/ml) at time points after start of IV NAC infusion commencement in the groups according to the severity of ADRs.

Data are reported as median and inter-quartile range (IQR).

Change in plasma tPA activity (u/ml) at time point Median (IQR)	Minimal ADRs (n=10)	Moderate ADRs (n=5)	Severe ADRs (n=6)
1h: 1.08 [1.00-1.16]	0.00 (-0.13-0.13)	0.00 (-0.20-0.80)	1.00 (0.23-1.15)
2h: 2.06 [2.00-2.18]	0.00 (-0.26-0.00)	0.00 (-0.05-0.15)	0.10 (0.00-0.30)
4h: 4.1 [4.0-4.3]	0.00 (-0.18-0.13)	0.00 (0.00-1.35)	-0.25 (-0.58-0.23)

5-4-2-9: Clotting factors and vWf factor

There was no association between plasma vWf and plasma clotting factor activity and severity of ADRs (see appendix 5.19 to 5.26 for raw data). Activity for the clotting factors II, VII, IX and X were, however, significantly decreased within 4h of NAC infusion commencement. Maximum derangement in factor II, IX and X occurred within an hour and for factor VII at 4h (Figure 5.3 and Table 5.11). There was significant correlation between plasma factor VIII and its carrier (plasma vWf) at baseline (r=0.4, p=0.05, n=22), at 1h (r=0.6, p=0.01, n=18) and at 2h (r=0.6, p=0.006, n=21).

Figure 5.3: Clotting factor activity (mean, iu/l) at baseline and time points (30min, 1h, 2h, 4h and 20h) after IV NAC infusion in patients with paracetamol overdose.

Activity of factor II (◊), factor VII (■), factor IX (●), and factor X (▲). Factors: II, VII, IX and X were significantly decreased compared to baseline within 4h of NAC infusion initiation (see also table 5.10 for details)

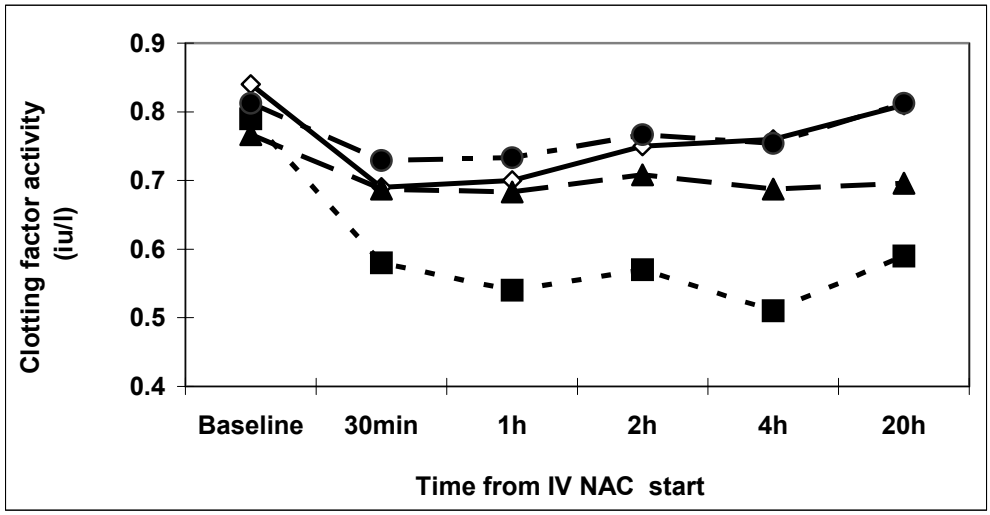


Table 5.11: Clotting factor activity (II, VII, IX, X, V, VIII, XI) (Median and IQR) at baseline and time points after IV NAC infusion commencement in patients with paracetamol overdose (n=22).

Time points: baseline and 30min, 1h 2h 4h and 20h after NAC infusion commencement. Activity of clotting factors in each time point were compared with factors at baseline. Clotting factor in each time point was compared with baseline using Mann Whitney U test. p is significance for paired comparison. Factors: II, VII, IX and X were significantly decreased compared to baseline within 4h after NAC infusion initiation. Factor VIII and XI did not change significantly. [a] n=22; [b] n=21; [c] n=20 ; [d] n=18; [e] n=19; [f] n=16,

Clotting factor activity (iu/l), time point Mean (95% CI)	Baseline (0)	30min	1h	2h	4h	20h
Factor II activity	0.84 (0.76-0.93) [a]	0.69 (0.60-0.77) [b] p=0.008	0.70 (0.60-0.80) [d] p=0.01	0.75 (0.67-0.84) [b] p=0.1	0.77 (0.67-0.86) [e] p=0.2	0.81 (0.68-0.94) [f] n=0.8
Factor VII activity	0.79 (0.45-0.70) [a]	0.56 (0.45-0.70) [d] p=0.05	0.54 (0.40-0.68) [d] p=0.02	0.57 (0.44-0.70) [b] p=0.04	0.51 (0.40-0.63) [d] p=0.006	0.59 (0.45-0.74) [f] p=0.09
Factor IX activity	0.99 (0.87-1.12) [a]	0.79 (0.68-0.90) [c] p=0.02	0.80 (0.67-0.93) [d] p=0.04	0.88 (0.71-1.06) [b] p=0.07	0.85 (0.72-0.97) [d] p=0.1	0.99 (0.81-1.16) [f] p=0.9
Factor X activity	0.88 (0.78-0.97) [a]	0.69 (0.61-0.76) [c] p=0.009	0.68 (0.59-0.78) [d] p=0.01	0.74 (0.62-0.85) [b] p=0.03	0.69 (0.61-0.78) [d] p=0.01	0.71 (0.60-0.81) [f] p=0.05
Factor XI activity	0.73 (0.64-0.81)) [a]	0.67 (0.60-0.75) [c] p=0.4	0.68 (0.58-0.77) [d] p=0.5	0.73 (0.61-0.84) [b] p=0.09	0.65 (0.57-0.73) [d] p=0.3	0.66 (0.57-0.75) [f] p=0.4
Factor V activity	0.69 (0.57-0.82) [a]	0.67 (0.56-0.79) [c] p=0.9	0.71 (0.56-0.86) [d] p=0.9	0.80 (0.65-0.94) [b] p=0.3	0.79 (0.64-0.93) [d] p=0.3	0.89 (0.71-1.07) [f] p=0.02
Factor VIII activity	1.31 (1.04-1.58) [a]	1.28 (0.91-1.05) [c] p=0.5	1.36 (0.95-1.77) [d] p=0.8	1.43 (1.05-1.81) [b] p=0.9	1.39 (1.11-1.68) [d] p=0.5	1.40 (1.22-1.57) [f] p=0.2

5-5:Discussion

NAC has been a treatment of choice in paracetamol overdose since its introduction in the 1970s [202;203]. Anaphylactoid reactions following IV NAC infusion were reported soon after its introduction [237;291], however the mechanism of the ADRs is not fully understood. The reported incidence of ADRs varies from 3% to 50% [231;239-241;243;292]. In the current study the incidence of anaphylactoid reactions was found to be 40.2% (10.1%: severe and 30.1% moderate). The discrepancy in ADRs incidence among different studies is likely due to variability in definition of ADRs, in mode of administration of NAC infusion (drip or pump), and possibly different study populations. The present study suggests that paracetamol concentration at the time of antidote use might be an important confounder.

Factors reported to increase the risk of anaphylactoid reactions to NAC, include history of asthma [237;244;245;293;294], atopy [295], drug allergy [245] and low plasma paracetamol concentration [239;241;245]. Female gender, family history of allergy and low paracetamol concentration were the only independent risk factors that were identified in the current study. It is unclear why asthma should be identified as a risk factor by Schmidt & Dalhoff, but not in this study. Whether there are differences in the genetic factors or other factors requires further studies.

During an anaphylactic reaction, mediators are released and can be detected in the blood soon afterwards. Histamine is detectable in plasma 10 minutes to 1h after reaction initiation [296;297]. Following bee sting histamine and tryptase have been shown to be in a significant association with clinical severity of anaphylactic reactions [250].

In man, a dose-dependent wheal and flare response to intradermal injection of Parvolex (the pharmaceutical branded preparation containing 200 mg/ml NAC together with EDTA [ethylene diamine tetra acetic acid] as a stabilizer and sodium hydroxide to correct pH) has been reported [247]. Pre-treatment with a specific H1 antagonist (terfenadine) suppressed the weal and flare response. NAC also caused dose-dependent histamine release from cultured mouse mast cell (PT18 cell line) and human basophils [248]. The authors suggested that ADRs to NAC might be attributed to a direct effect on mast cell and basophils. An in vitro study [298] showed that NAC induced spontaneous histamine release from human peripheral leukocytes. The main finding of the current study was a higher histamine concentration in the group with severe ADRs. Adding this finding to the previous studies findings, it seems clear that histamine is involved in mediating ADRs following IV NAC infusion; however this is not primarily due to variability in NAC concentration as there was no difference in NAC concentration between groups (Table 5.7).

The measurement of plasma tryptase along with plasma histamine has been suggested for the diagnosis of anaphylaxis and change can be detected 1 to 2 hours after initiation of anaphylactic responses [297]. In this study no relationship was found between ADRs severity and change in plasma tryptase (Table 5.9). These findings suggest either very low levels of release from mast cells, or more likely, that the source of histamine was basophils which have far lower tryptase levels [299].

Endothelial injury and activation of the coagulation system occurs in anaphylaxis [300-302]. An elevation in vWf factor, a marker of endothelial injury, has been reported in anaphylactic shock [251]. A study on healthy volunteers receiving therapeutic doses of NAC showed a rapid increase in factor VIII and its carrier, vWf factor, in the group with anaphylactoid reactions but not in the group without ADRs [231]. In the present study there was no association between changes in the activity of clotting factors and vWf and severity of reaction. Furthermore, vWf did not correlate with histamine. It is possible that the presence of paracetamol or recent paracetamol overdose may accounts for this difference, but further studies are required to understand the reason for the difference in adverse effects profile.

As reported by others there was a significant fall in vitamin K dependent clotting factor activity (II, VII, IX and X) in all subjects within 1 to 4h of NAC infusion commencement (Figure 5.3 and Table 5.11) [302]. While this may be relevant

to the diagnosis of hepatotoxicity following paracetamol overdose there was no relationship to ADR occurrence. There was a significant correlation between factor VIII activity and its carrier, vWf factor, confirming previous findings [231].

Anaphylaxis also activates the fibrinolytic system, an effect thought to be due to release of mast cell products, resulting in endothelial cell stimulation [302-306] . In a study on subjects with anaphylactic shock after insect sting challenge both tPA, a marker and fibrinolytic injury, and vWf, a marker on endothelial injury, increased within a few minutes of onset of clinical symptoms [251]. In this study the effects on tPA were not significant when AUC of response was examined, suggesting this mediator is not a primary factor in this adverse reaction. In vitro studies have shown that toxic, but not therapeutic, doses of paracetamol inhibit the function of lymphocytes, [307] neutrophils, [308] and platelets [309]. The suggested mechanism is thought to be paracetamol-induced reversible cyclo-oxygenase inhibition, resulting in reduction in PG and thromboxane synthesis, indicating that paracetamol may perhaps have some specific mast cell effects. Since PG is a key mediator in anaphylactic reactions [309], its inhibition by paracetamol might play a role in preventing ADRs to NAC . The present data showed an inverse relationship between plasma paracetamol and severity of ADRs, which also confirms the results of other studies, suggesting that higher concentrations of paracetamol are protective against anaphylactoid reactions to NAC. More studies are required to elucidate the effect of paracetamol on PG synthesis, mediator release and inhibiting anaphylactoid reactions.

It thus appears that NAC-induced histamine release in paracetamol overdose occurs in the absence of release of other traditional markers of mast cell degranulation or endothelial dysfunction. The source of histamine therefore seems most likely to be from basophils, which have lower tryptase content. The protective role of paracetamol implies a pharmacological effect on the mechanisms involved in the ADR process. The most likely target would seem to be cyclo-oxygenase. In a previous study discussed in this thesis it was hypothesized that paracetamol effects on renal potassium loss in overdose are due to inhibitory effects of paracetamol on cyclo-oxygenase [273]. In vitro data suggests that NAC may modulate PG synthetic pathways, promoting bronchoconstriction by increasing synthesis of PGF2 alpha and reducing synthesis of bronchodilator PGE [298]. Although asthma was not a predominant feature a significant minority of patients had bronchoconstriction, which is in keeping with this hypothesis.

In the intensive study one patient (subject number one, see appendix 5.11) who had severe vomiting with no obvious features of anaphylactoid reaction in whom NAC infusion was stopped also had an increase in plasma histamine concentration within 30min after infusion, which was 5 times higher (2.44 ng/ml) than baseline (0.48 ng/ml) level. Other subjects with ADRs showed combinations of vomiting and feature of anaphylactoid reactions and it is therefore unclear whether the release of histamine contributes to the nausea

caused by this antidote. The rates of nausea and vomiting observed in this study were high and this raises the issue of whether routine anti-emetic prophylaxis with an antihistamine would be effective and if histamine release is involved in their causation. The ADR profiles illustrate the inter- individual susceptibility to different ADR features. The reasons for this variability also require to be understood if the incidence of ADRs to NAC is to be reduced. There appear to be other individual factors that underlying the risk of having an ADR to NAC, and family history of allergy and gender effect suggest that genetic factors may be relevant here. Whether reducing the initial bolus dose of NAC or prolongation of loading dose infusion would reduce the incidence of adverse effects without impairing efficacy are other key questions to be clarified.

6-6: Conclusion

Anaphylactoid reactions to acetylcysteine are relatively common in patients with paracetamol overdose. Low paracetamol concentration is a risk factor in developing ADRs. Histamine release is associated with the reaction severity. Future study is required to elucidate the specific effects of paracetamol that protects against ADRs to its antidote and these seem likely to involve inhibition of PG synthesis. The involvement of histamine in the reaction raises the possibility that pre treatment with antihistamine could be protective.

Chapter VI: Discussion

6-1: Summary of the thesis

Paracetamol has been available as an over-the-counter drug (without prescription) since 1956, with a remarkable safety record at normal therapeutic doses. Although it has been used for more than 50 years, there are still many unknown aspects in regards to its toxicity and treatment in overdose. The first toxicity of paracetamol in overdose in man was reported in 1966 [41;42]. It is the most commonly used drug in deliberate self harm [43-46] being involved as a component in 48% of poisoning admissions to hospital in the UK [47]. Paracetamol is the commonest cause of fulminant hepatic failure and liver transplantation in the UK and the US [40;51-57]. Renal insufficiency during the course of paracetamol overdose, with or without concomitant hepatic failure, has also long been recognised [42;81-90]. However, the mechanism of the nephrotoxicity in man is not fully understood.

The main pharmacological effect of paracetamol is inhibition of cyclo-oxygenase (COX) and thus prostaglandin (PG) synthesis [6]. In overdose non-steroidal anti-inflammatory drugs such as ibuprofen, cause dose-dependent increase in urinary potassium excretion (FeK) and sodium retention [262], probably due to vasoconstriction. It was therefore hypothesised that paracetamol in overdose may affect renal function due to similar mechanisms.

To examine this hypothesis the effect of acute paracetamol overdose on plasma and urinary electrolytes was investigated retrospectively, and more intensively prospectively (Chapter II). The results of these studies showed paracetamol overdose is associated with dose-related hypokalaemia, and kaliuresis of short duration (less than 24 h post-ingestion). A previous study also showed hypophosphatemia and dose-dependent phosphaturia following paracetamol overdose [198], but this effect of paracetamol overdose on potassium handling has not been previously reported. The findings of the current and previous studies suggest a specific renal effect of paracetamol in overdose. This is likely to be due to inhibitory effect on COX and PG synthesis.

Liver failure is a well-known toxic effect of serious paracetamol overdose. Renal failure is less common than liver failure and occurs in only 1% of all patients with paracetamol overdose. This has been reported to reach 10% in severe paracetamol poisoning [18;91;270]. In most cases kidney failure occurs concomitantly with liver failure, although isolated kidney damage following paracetamol overdose has been reported [87;89;90].

In the third chapter of this thesis the frequency of renal failure, the associated risk factors of renal injury and impact of kidney damage on outcomes in a large cohort of patients who developed liver failure following paracetamol overdose were examined. The results of the study showed that whereas renal impairment is known to be relatively uncommon after mild to moderate paracetamol

overdose, it was a common complication in patients referred to a tertiary centre following severe paracetamol poisoning. Important associated factors in predicting poor outcome were hypotension, higher plasma creatinine concentration, raised GGT and concomitant liver dysfunction at first presentation to hospital. Presentations to hospital more than 24 h post-ingestion and staggered overdose are also poor prognostic factors. However, the population studied was from a single large UK centre and may therefore not be an accurate reflection of patients in other liver units around the world.

In these patients with severe paracetamol overdose the relationship between time of presentation and plasma electrolytes at presentation was examined. This analysis showed that paracetamol overdose had time-dependent effects on potassium. In the earlier stages (within 24 h), plasma potassium fall is in a dose-related association with plasma paracetamol concentration, probably due to pharmacological effect of paracetamol in the kidney described in chapter three. In the later stage of toxicity, rise in plasma potassium is associated with rise in plasma creatinine concentration secondary to the nephrotoxic effect of paracetamol. Thus different mechanisms for changes in plasma potassium exist at different time after poisoning. The finding of the prospective study in the chapter 3 of the thesis showed kaliuresis. This suggests that fall in plasma potassium in the earlier stage is due to renal loss, possibly due to inhibitory effect of paracetamol on cyclo-oxygenase which alters renal hemodynamics and

tubular handling of electrolytes. Later changes in plasma potassium are likely due to direct nephrotoxic effects of paracetamol.

In the fourth and fifth chapters the focus of the thesis was on antidote treatment of paracetamol poisoning. Acetylcysteine (NAC) has long been used as a treatment of choice for the treatment of paracetamol overdose in patients who are at risk of hepatotoxicity. There have been reports of liver failure and death in patients who had plasma paracetamol concentration below the current UK treatment threshold nomogram, and who are therefore not treated [218].These authors suggested lowering the current UK treatment threshold line. The report generated controversy with both support [219] and criticism of the suggested policy change [220;221;223;283]. To establish the numbers of patients presenting with severe liver dysfunction when initial paracetamol concentrations are below the current nomogram level, a systemic retrospective study survey on patients presenting to two tertiary liver centres due to suspected liver failure following paracetamol poisoning was performed in defined geographic area over a specific time. The findings of the study showed that this event occurs only in a very small proportion of patients. In the view of the rarity of the event, the costs of therapy and risk of adverse reactions (ADRs) the study concluded that it is unnecessary to lower the current UK threshold for antidote therapy in paracetamol overdose.

One other important problem in the management of paracetamol overdose is ADRs to intra venous infusions of NAC. The current protocol for antidote therapy in paracetamol poisoning in the UK is the Prescott protocol [203]. Intravenous infusion of NAC causes adverse reactions in some patients [237].The frequency of such reactions, varies from 3-9% [238-240] to 48.4% [241] in different studies. Some factors including asthma [244;245] and low paracetamol concentration [239;241;245] have been reported to associated with ADRs. The patterns and mechanisms of ADRs in man are not well described or understood. A non-allergic release of histamine has been suggested as a potential mechanism of ADRs [247]. In the last two studies described in the thesis (chapter VI) the frequency, risk factors and mechanisms of ADRs to NAC were examined. In a prospective study the factors that influence frequency of ADRs were studied. In a smaller intensive study the role of histamine and other biomarkers as underlying pathophysiological mechanisms in the ADRs were explored. The results of these studies showed that nausea and vomiting (mild ADRs) occurred in 60% of the patients, and anaphylactoid reactions (moderate and severe ADRs) in 40%. Plasma paracetamol concentration at the time of admission and male gender were protective, and having family history of allergy was a risk factor in developing ADRs to NAC. The results of the intensive study showed the severity of ADRs was associated with higher plasma histamine, and lower plasma paracetamol concentrations. In this study plasma tryptase and other markers of anaphylaxis and anaphylactoid reactions did not change significantly. This may suggest a non-mast cell source for the release of histamine, possibly

from circulating basophils, which have low levels of tryptase. A relationship between paracetamol concentration and severity of ADRs has already been reported in the literature [231;239], but this is the first time histamine rise in plasma has been shown to be an underlying mechanism of ADRs to NAC in man, and related to degree of severity. It is possible that inhibitory effect of paracetamol on cyclo-oxygenase and PG synthesis, which are important mediators in anaphylactoid reactions, may contribute to the protective effect of paracetamol against ADRs to NAC.

6-2: Conclusion

From the work presented in this thesis it is possible to draw the following conclusions:

1. Paracetamol overdose is associated with dose-related hypokalaemia, and kaliuresis of short duration (<24 h), suggesting a specific renal effect of paracetamol in overdose perhaps via cyclo-oxygenase and prostaglandin synthesis inhibition. This effect seems distinct from any nephrotoxic effect of paracetamol.

2. Creatinine at first admission appears to be a predictor of poor outcome in paracetamol overdose. A better understanding of mechanisms involved in causing renal dysfunction may offer potential therapeutic targets for improving

outcomes in this common poisoning. Additionally, staggered overdose, liver dysfunction, raised GGT and hypotension at first admission are also risk factors of both renal injury and poor prognosis.

3. Liver dysfunction following overdose causing plasma paracetamol concentrations below the current UK treatment threshold occurs in very small percentage of patients with paracetamol overdose. Thus in view of the rarity of this event, the work reported here does not suggest that lowering the current thresholds for antidotal treatment is likely to be cost-efficient.

4. ADRs to IV NAC predominantly involve the gastrointestinal (GI) and respiratory system and skin. Chest pain was also a feature observed. GI involvement is more common and the reaction is often mild. More severe ADRs are associated with rash, bronchospasm and chest pain. The severity of ADRs correlates with the extent of histamine release as measured in plasma. Histamine release in the patients studied appeared independent of tryptase release, suggesting a non-mast cell source. Paracetamol is protective against adverse effects of NAC, suggesting a mechanism involving inhibition of PG synthesis.

6-3: Weaknesses of the thesis

The studies presented in this thesis had the following weakness:

1. The thesis presents studies on the theme of paracetamol overdose.
Studies in this area are challenging due to the nature of the population involved. The recruitment rate was often slow and the study groups often thus smaller than originally conceived.

2. Some of the studies were retrospective and therefore there was a limited control on collection of required information. Clinical assays vary from time to time and place to place which could affect the conclusions in the retrospective cohorts studied. However, the large numbers involved will tend to reduce the impact of this.

3. In the prospective studies the number of subjects who eventually completed the whole study or in part was small. This was due to difficult population involved, and complexity and time dependent nature of the design of the studies.

4. The studies have been conducted on a Scottish population, and therefore the results might not be generally reproducible to other population due to difference in cultural factors, genetic factors and social habits, including in particular alcohol consumption.

5. In the NAC intensive study, due to the nature of study most patient were recruited during the daylight when patients who present later after ingestion tend to be admitted and therefore have lower plasma concentrations. As this was found to be a risk factor in developing adverse reactions to NAC this may be a confounder. Thus the frequency of ADRs to NAC in this group was not an accurate reflection of all paracetamol admissions to hospital who received NAC following overdose, as is shown from the larger cohort studied. Sample collection and handling in a clinical environment also present challenges that might have affected sample stability, although careful steps were taken to minimise this risk.

6-4: Further studies

The findings of this thesis suggest following futures studies:

1. Further studies are required to measure the effect of paracetamol overdose on renal function and hemodynamics using more sensitive surrogate markers of renal injury. Measurement of renal PG, aldosterone and plasma renin activity would also give us a better understanding of renal effects of paracetamol in overdose.

2. Further studies on healthy volunteers are required to examine the effect of NAC on kidney function.

3. Further studies are required to examine whether more subtle biomarkers of renal dysfunction such as urinary enzymes biomarkers can be used as predicting factors of renal injury at early stage of renal impairment following paracetamol overdose, and whether these biomarkers are useful in predicting liver injury.

4. Further studies are required for greater understanding of mechanisms of paracetamol nephrotoxicity in severe paracetamol poisoning and whether the renal injury is an independent phenomenon or as consequence of liver damage.

5. Further studies at the molecular level are required to elucidate the specific effects of paracetamol on PG synthesis and its relationship with histamine release in anaphylactoid reactions to IV NAC.

6. Further study is required to investigate the frequency of ADRs on patients with paracetamol overdose who are pre-treated with antihistamine and antiemetics before receiving antidote treatment.

7. Further studies are required to investigate the underlying mechanisms of anticoagulant properties of paracetamol and NAC.

Index

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Appendices

List of Contents of Appendices

Appendix 2.1: Patient invitation letter

Version3, 19/07/04
Ref No: 04/s1101/20

Renal Function Study-Patient invitation letter
Researcher: Dr. Nasrin Pakravan

Dear Sir/Madam

You are being asked to take part in a study in which we are examining how certain drugs affect kidney function. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the information will be given you carefully and ask if there is anything that is not clear or you would like more inform. If you wish not to take part in this study, it will not affect your treatment. Thank you for your time.

Yours Faithfully,

Dr Nasrin Pakravan MD

Clinical Research Fellow

Appendix 2.2: Patient Information Sheet

Version1, 25/05/04
Ref No: 04/s1101/20

Renal Function Study-Patient Information Sheet
Researcher: Dr. Nasrin Pakravan

You are being asked to take part in a study in which we are examining how certain drugs affect kidney function, and would be grateful of your help.

It is thought that overdose of some drugs such as paracetamol (Panadol), ibuprofen (Brufen) and some antidepressants can adversely affect the way kidneys work, and by measuring marker substances in blood and urine we may be able to predict this, and therefore protect the kidney. A greater understanding of this process may be a useful step in improving care of overdosed patients in general.

You are being asked to take part in study as you have taken an overdose of one of these drugs. The actual risk of you suffering kidney damage is small, but your results will assist us in determining the best markers to use for predicting kidney problems.

If you agree to take part in this study, you will be asked to allow us to use the routine urine and blood samples taken when you were admitted for this research, and to provide an extra blood and urine sample at 12 hours and 24 hours after ingestion for more investigations to guide your care. We are also asking your permission to use these clinical samples for research. To evaluate your kidney's function accurately we need to check your blood pressure and pulse rate regularly.

Blood samples will be taken either by one of the nursing staff or myself. All the results will be kept anonymous, and your personal details will not be disclosed to a third party.
We also inform your general practitioner (GP) of this study, unless you object to this.

Thank you for reading this information sheet. Please ask if you have any questions.

Dr Nasrin Pakravan

Clinical Research Fellow

Appendix 2.3: GP Information Letter

Version1, 25/05/04
Ref No: 04/s1101/20

Renal function: study-GP Information Letter
Researcher: Dr. Nasrin Pakravan

Dear Dr. ……

I am a Ph-D medical student doing a research study on patients with certain kinds of drug overdose, including paracetamol, ibuprofen and SSRIs to evaluate their effect on kidney function.

I am writing to inform you that Mr/ Mrs…….
who was admitted to the toxicology ward of Royal Infirmary of Edinburgh with an overdose of one of these drugs, with his/her permission provided samples of urine and blood for this study. The study has not involved any additional medication on his/her treatment.

Yours Faithfully,

Dr Nasrin Pakravan MD

Clinical Research Fellow

Appendix 2.4: Patient's Consent Form

Version 1
15/04/04

Renal function: Patient's Consent Form
Researcher: Dr. Nasrin Pakravan

Patient's Name: ……..

I have read and understood the patient information regarding the above study, and agree to take part. I understand that this will involve me providing up to three blood and urine samples in addition to routine samples being taken during my time in hospital. In addition my blood pressure and pulse rate will be recorded regularly at hourly intervals, which is more frequently than would otherwise be the case. I realized that I can withdraw my consent at any time, without giving any reason, and it will not affect my Clinical care. I also agree that my GP may be informed.

Signed: …… **Date**

Witnessed: …… **Date**

Appendix 2.5: Data Collection Sheet

Patient Data Collection Sheet
Renal Function Study In Drug Overdose

Study Ref Number: 04/S1101/20
Clinical Research Fellow: Dr Nasrin Pakravan
1: Patient's ID
2: Patient's height
3: patient's weight:
4: Date of admission
5: time of admission of Ingestion
6: Date of ingestion
7: time of ingestion
8: Admission to A&E CAB6
9: Name of tablet taken Paracetamol and other preparations
SSRI (Fluoxetine, Paroxetine)
Others
10: Number of tablet taken
11: Vomit after taking the tablet
12: Co-ingestion of alcohol with drug before or after drug ingestion No YES
13: Underlying disease Diabetes Chronic renal disease Chronic heart disease
Chronic liver disease Other
14: Drug history
15: Initial Vital sign Blood Pressure Pulse rate
Respiratory Rate Temperature
16: Samples to be taken at 4h post-ingestion

Biochemistry: Blood sample (5cc in orange top tube) at 4h post-ingestion date &time
Urine sample (10 cc in universal container)

17: Samples to be taken at 12h post-ingestion

Biochemistry: Blood sample (5cc in orange top tube) at 4h post-ingestion date & time:
Urine sample (10 cc in universal container) date & time

18: Samples to be taken at 24h post-ingestion

Biochemistry: Blood sample (5cc in orange top tube) at 4h post-ingestion date & time: Urine sample (10 cc in universal container) date & time

19: NAC treatments YES NO
20: Vomit after over hospital stay
21: Blood pressure and PR at 4h 12h 24h date &time
22: Hypotension over hospital stay YES NO

Study Guideline

Study Ref No: 04/s1101/20

Project Title

Effect of single paracetamol overdose on renal function and plasma and urine electrolytes

Clinical Research Fellow

Dr Nasrin Pakravan

Subjects

Inclusion Criteria

-Single overdose with paracetamol, ibuprofen, fluoxetine, and benzodiazepines.

-Mixed overdose of each of this drug with benzodiazepines or alcohol

-Patients admitted 4 or less than 4 hours after ingestion

-Age 16 years and older

-Non-pregnant patients

Exclusion Criteria

-Patients under 16 and over 60 years old

-Pregnant women

-Patients with inability to read and understand the information sheet and consent forms

-Patients with underlying disease: Diabetes mellitus, chronic renal failure, Chronic heart failure, hypertension, hypovolaemic shock

-Mixed overdose with other drugs except with benzodiazepines or alcohol

-Unknown time of overdose or admission more than 4 hours after ingestion

Appendix 2.7: Study Flow chart

Study Flow chart

Patient Admitted in A&E/ Toxicology Ward

↓

Invitation
Information sheet

↓

Obtaining consent

↓

Patient data collection sheet

↓

4-hr post-ingestion samples

For Biochemistry (use labels provided for biochemistry)	- **5 cc blood sample** in orange top tube -**10 cc urine sample** in universal container

↓

12 hr- post-ingestion samples

For Biochemistry (use labels provided for biochemistry)	-**5 cc blood sample** in orange top tube -**10 cc urine sample** in universal container

↓

take 24 hr- post-ingestion samples

For Biochemistry (use labels provided for biochemistry)	-**5 cc blood sample** in orange top tube -**10 cc urine sample** in universal container

Appendix 2.8: Original data of patients with single paracetamol overdose (Retrospective study), n=155.

Code	DOB	DOA	Sex	Age y	Type of OD	4h para	Sali	Cr1	Na1
1	24.03.1970	24.09.2005	M	35.53	single od	259	0	97	140
2	28.12.1950	07.09.2002	F	51.73	single od	524	.	92	133
3	24.02.1962	29.08.2003	F	41.54	single od	382	.	64	138
4	24.07.1984	26.10.2005	F	21.27	single od	288	0	60	137
5	06.11.1956	09.04.2006	M	49.45	single od	238	0	76	134
6	19.07.1983	18.12.2004	F	21.43	single od	105	0	60	141
7	24.05.1985	03.04.2006	F	20.87	single od	207	0	77	140
8	20.05.1982	16.03.2002	F	19.84	single od	106	.	88	135
9	23.08.1977	11.01.2002	F	24.4	single od	405	0	99	136
10	13.09.1980	27.04.2004	F	23.64	single od	260	0	66	138
11	13.09.1980	16.01.2005	F	24.36	single od	179	0	75	141
12	28.03.1960	05.01.2002	M	41.8	single od	178	.	75	136
13	19.01.1962	19.02.2004	M	42.11	single od	180	.	88	137
14	19.01.1962	16.05.2004	M	42.35	single od	138	0	106	141
15	24.02.1985	02.02.2004	F	18.95	single od	125	.	76	138
16	07.12.1973	11.09.2005	F	31.78	single od	179	0	75	142
17	10.03.1955	09.02.2003	F	47.95	single od	226	.	72	137
18	11.06.1974	10.10.2004	F	30.35	single od	504	0	75	134
19	23.03.1968	31.10.2005	M	37.63	single od	148	0	76	137
20	23.03.1968	02.11.2005	M	37.64	single od	155	0	79	139
21	23.03.1968	06.11.2005	M	37.65	single od	123	0	72	140
22	23.03.1968	09.11.2005	M	37.66	single od	136	0	70	142
23	23.03.1968	04.12.2005	M	37.73	single od	117	0	82	142
24	25.05.1984	04.07.2002	F	18.12	single od	222	.	70	139
25	14.12.1962	06.03.2006	F	43.25	single od	446	0	77	140
26	30.11.1957	07.12.2003	M	46.05	single od	346	0	114	137
27	07.02.1979	15.08.2002	M	23.53	single od	151	0	102	141
28	27.09.1977	12.07.2004	M	26.81	single od	207	0	101	143
29	30.07.1973	06.07.2003	M	29.95	single od	76	0	99	138
30	01.11.1974	27.05.2003	M	28.59	single od	194	0	90	138
31	22.10.1995	19.09.2003	M	7.92	single od	95	0	91	139
32	22.07.1988	25.01.2005	F	16.52	single od	368	0	86	142
33	22.07.1988	15.03.2005	F	16.66	single od	463	.	84	144
34	19.11.1962	28.10.2005	F	42.97	single od	72	.	78	145
35	26.11.1942	11.04.2002	F	59.41	single od	208	.	84	133
36	26.02.1958	15.01.2005	F	46.92	single od	133	0	59	141
37	10.08.1968	10.04.2004	M	35.69	single od	92	0	76	138
38	01.08.1958	14.12.2002	M	44.4	single od	288	0	96	138
39	13.05.1961	20.12.2003	F	42.63	single od	138	0	73	140
40	11.07.1949	02.03.2002	M	52.68	single od	89	.	84	137
41	21.05.1946	25.10.2002	F	56.47	single od	135	0	75	135
42	29.04.1987	07.11.2005	F	18.54	single od	255	0	69	141
43	06.02.1960	15.11.2003	M	43.8	single od	176	0	87	138
44	05.05.1963	16.04.2003	F	39.98	single od	92	0	93	136
45	08.08.1941	20.10.2004	F	63.24	single od	261	0	80	129
46	22.01.1946	14.08.2002	F	56.6	single od	156	.	85	134
47	16.02.1981	04.10.2003	M	22.64	single od	100	0	99	141
48	24.07.1972	08.04.2006	M	33.73	single od	233	0	93	140

Code	DOB	DOA	Sex	Age y	Type of OD	4h para	Sali	Cr1	Na1
49	05.09.1972	13.08.2003	F	30.96	single od	206		75	140
50	22.11.1984	02.10.2003	F	18.87	single od	237		77	139
51	10.11.1982	14.01.2006	F	23.19	single od	372	0	79	137
52	22.03.1955	15.11.2004	M	49.69	single od	74	0	102	142
53	15.05.1984	09.04.2006	F	21.92	single od	63	0	85	143
54	18.07.1976	31.08.2004	F	28.14	single od	239		78	140
55	02.12.1963	20.03.2002	F	38.32	single od	132		78	139
56	02.12.1963	21.02.2004	F	40.25	single od	137	0	67	143
57	28.08.1980	14.02.2003	M	22.48	single od	115		91	141
58	24.06.1968	24.04.2002	F	33.85	single od	468		97	140
59	27.08.1980	07.09.2004	M	24.05	single od	108	0	96	142
60	23.08.1965	09.02.2005	F	39.49	single od	388	0	81	145
61	10.06.1981	01.03.2002	M	20.74	single od	247		95	142
62	17.09.1961	28.12.2004	M	43.31	single od	163	0	126	143
63	09.06.1971	15.03.2003	M	31.79	single od	149	0	95	133
64	07.12.1987	31.01.2005	M	17.16	single od	173	0	102	142
65	07.03.1973	10.09.2002	M	29.53	single od	201	0	79	139
66	16.01.1969	06.10.2002	M	33.74	single od	125		88	137
67	07.09.1972	25.12.2003	F	31.32	single od	122	0	108	139
68	08.10.1986	18.04.2004	F	17.54	single od	260		73	141
69	08.10.1986	21.04.2004	F	17.55	single od	242		71	138
70	08.10.1986	15.05.2004	F	17.61	single od	265	0	79	142
71	08.10.1986	20.05.2004	F	17.63	single od	258		83	140
72	08.10.1986	27.07.2004	F	17.81	single od	148		78	140
73	04.10.1965	13.05.2002	F	36.63	single od	222	0	82	139
74	26.06.1983	29.07.2003	M	20.1	single od	110		86	136
75	20.05.1967	19.09.2002	F	35.36	single od	340		81	139
76	29.08.1966	18.05.2003	M	36.74	single od	395		91	135
77	21.03.1987	01.06.2004	F	17.21	single od	34		79	139
78	01.08.1963	21.11.2003	M	40.33	single od	55	0	90	140
79	13.06.1973	29.06.2003	F	30.06	single od	141		77	137
80	22.03.1984	11.03.2006	F	21.98	single od	224	0	5.5	140
81	11.08.1983	19.04.2005	M	21.7	single od	242	0	88	143
82	09.12.1985	01.12.2003	F	17.99	single od	74		78	136
83	27.01.1986	03.11.2003	F	17.78	single od	176		86	141
84	07.10.1958	12.01.2006	F	47.3	single od	157	0	80	139
85	27.10.1961	24.04.2002	F	40.52	single od	300		78	139
86	27.10.1961	02.08.2002	F	40.79	single od	353		72	138
87	27.10.1961	29.04.2003	F	41.53	single od	202	0	56	139
88	27.10.1961	17.09.2003	F	41.92	single od	125	0	77	143
89	02.06.1968	03.04.2006	F	37.86	single od	208	0	67	142
90	11.01.1980	20.10.2003	M	23.79	single od	277		75	141
91	07.07.1976	03.09.2003	M	27.18	single od	147	0	91	145
92	02.03.1976	14.12.2005	F	29.81	single od	84	0	89	141
93	05.11.1950	05.12.2002	M	52.12	single od	72	0	84	138
94	28.04.1959	05.09.2004	F	45.39	single od	190	0	78	134
95	28.04.1986	19.11.2002	F	16.57	single od	70		69	137
96	25.03.1980	01.07.2004	F	24.28	single od	233		93	140
97	03.03.1985	16.07.2005	F	20.38	single od	175	0	89	143
98	28.09.1966	30.08.2002	M	35.95	single od	113	0	83	140

Code	DOB	DOA	Sex	Age y	Type of OD	4h para	Sali	Cr1	Na1
99	05.06.1987	01.05.2005	F	17.92	single od	111	0	72	140
100	11.11.1980	27.03.2003	M	22.39	single od	316	0	92	145
101	02.08.1963	16.03.2003	F	39.65	single od	121	0	84	142
102	02.08.1963	08.12.2005	F	42.38	single od	147		85	145
103	02.08.1963	09.08.2005	F	42.05	single od	107		80	143
104	23.05.1967	30.05.2003	F	36.04	single od	249		64	137
105	04.08.1988	01.05.2003	F	14.75	single od	101	0	86	139
106	28.03.1957	19.01.2003	F	45.84	single od	254		79	141
107	12.03.1956	10.02.2003	M	46.95	single od	127		90	135
108	19.09.1976	29.08.2004	M	27.96	single od	230	0	81	131
109	19.09.1969	21.09.2004	F	35.03	single od	266	0	82	139
110	19.09.1969	12.10.2004	F	35.09	single od	198	0	80	137
111	12.07.1988	15.10.2004	F	16.27	single od	117	0	76	142
112	12.07.1968	18.10.2004	F	36.29	single od	120	0	73	140
113	03.02.1965	23.03.2005	M	40.16	single od	180	.	85	135
114	25.02.1982	06.08.2003	F	21.46	single od	205	.	81	138
115	13.06.1975	08.09.2002	M	27.26	single od	119	0	88	140
116	13.06.1975	09.10.2003	M	28.34	single od	222	0	84	144
117	04.06.1983	20.11.2005	M	22.48	single od	192	0	91	145
118	03.09.1979	05.04.2003	F	23.6	single od	279	0	76	137
119	05.12.1970	02.03.2006	F	35.26	single od	420		72	138
120	24.07.1984	12.04.2005	F	20.73	single od	285	0	68	141
121	01.09.1958	01.11.2002	F	44.2	single od	233		83	138
122	27.12.1982	26.01.2005	M	22.1	single od	67	0	97	141
123	25.02.1972	18.09.2002	M	30.58	single od	148		77	140
124	13.10.1984	17.11.2002	F	18.11	single od	190		82	141
125	06.07.1967	27.03.2003	M	35.75	single od	35	0	111	139
126	23.08.1966	23.04.2006	F	39.69	single od	224	0	69	136
127	02.11.1971	10.12.2003	F	32.13	single od	199	0	85	138
128	24.03.1970	21.01.2005	M	34.85	single od	153	0	101	139
129	24.03.1970	22.11.2005	M	35.69	single od	119	0	88	138
130	25.09.1967	09.04.2006	F	38.56	single od	180	0	76	138
131	26.06.1984	18.11.2005	F	21.41	single od	172	0	81	141
132	24.04.1958	18.05.2003	F	45.1	single od	160		84	146
133	23.11.1968	14.07.2005	M	36.66	single od	75	0	103	139
134	16.04.1950	20.03.2005	F	54.96	single od	39	0	63	141
135	05.07.1976	26.07.2002	M	26.07	single od	176		101	138
136	06.08.1985	14.11.2004	F	19.29	single od	282	0	75	144
137	20.05.1977	21.10.2002	F	25.44	single od	150		95	141
138	06.06.1973	26.06.2005	F	32.08	single od	139	0	73	133
139	16.10.1971	16.05.2005	M	33.61	single od	127	0	90	140
140	05.10.1956	02.08.2003	F	46.85	single od	176		80	134
141	05.10.1956	03.04.2005	F	48.53	single od	238	0	74	139
142	05.10.1956	21.05.2005	F	48.66	single od	156	0	81	135
143	05.10.1956	26.08.2005	F	48.92	single od	118	0	66	142
144	09.10.1966	08.05.2002	M	35.6	single od	185	0	106	135
145	12.05.1976	16.08.2002	F	26.28	single od	247		86	141
146	12.05.1976	06.09.2002	F	26.34	single od	226		82	143
147	30.09.1971	16.01.2004	M	32.32	single od	326	0	77	142

Code	DOB	DOA	Sex	Age y	Type of OD	4h para	Sali	Cr1	Na1
148	16.09.1963	22.08.2004	M	40.96	single od	231	0	79	134
149	17.10.1981	26.04.2004	F	22.54	single od	127	0	77	139
150	08.10.1986	19.05.2004	F	17.62	single od	258		83	140
151	08.10.1986	18.04.2005	F	18.54	single od	260		73	141
152	08.10.1986	15.05.2006	F	19.61	single od	265	0	79	142
153	18.04.1973	26.04.2005	F	32.04	single od	244	0	87	141
154	16.09.1967	20.03.2004	M	36.53	single od	292	0	86	139
155	22.06.1985	31.03.2002	M	16.78	single od	244		101	138

Code	K1	TCO21	Cr2	Na2	K2	TCO22	DT	NAC	Vomit
1	3.8	22	91	.	3.2	24	19	YES	YES
2	4.1	25	105	126	3.6	20	19	YES	YES
3	3.2	20	60	138	2.8	26	33	YES	YES
4	3	19	71	135	3.5	20	26	YES	YES
5	3.5	22	88	135	3.2	20	19	YES	YES
6	3.8	24	58	140	3.6	25	22	YES	NO
7	3.5	18	77	140	3.4	25	22	YES	YES
8	3.7	19	82	142	3.3	30	23	YES	YES
9	3.4	17	96	138	3.1	21	21	YES	YES
10	3.6	22	66	139	2.9	26	20.5	YES	YES
11	3.4	24	60	141	3.1	26	23	YES	YES
12	3.7	23	75	139	3.6	28	12.5	NO	YES
13	3.6	25	81	140	3.8	28	23	YES	NO
14	3.4	21	103	141	3.4	27	13.5	YES	YES
15	4.1	19	73	136	3.8	25	22	YES	YES
16	4	26	75	139	3.5	25	13	NO	NO
17	4.1	24	73	137	3.2	26	24	YES	YES
18	4.4	20	68	136	4.4	17	24	YES	NO
19	3.9	24	80	140	3.9	23	22	YES	YES
20	3.9	24	72	138	3.3	25	23	YES	YES
21	4.4	21	74	139	3.8	23	22	YES	YES
22	3.5	22	75	138	3.8	28	18	NO	YES
23	4.7	26	71	139	3.7	27	24	YES	YES
24	3.6	24	88	142	3.4	26	23	YES	YES
25	4.6	24	78	138	3	21	31	YES	YES
26	4	24	76	137	3.6	26	26	YES	YES
27	4.4	22	83	136	3.5	27	23.5	YES	NO
28	4.1	21	94	139	4.2	30	24	YES	YES
29	4.1	25	94	138	3.5	31	21	YES	YES
30	4.1	25	90	137	3.8	26	19	YES	NO
31	3.4	21	98	138	4.1	23	11	YES	YES
32	3.5	21	81	137	2.9	26	20	YES	YES
33	4.2	26	73	140	3	25	24	YES	NO
34	4.2	23	65	140	3.9	24	25	YES	NO
35	2.8	21	73	136	3.5	27	24	YES	YES
36	3.4	28	60	138	2.9	31	24	YES	NO
37	4	19	77	138	3.4	24	19	YES	YES
38	3.9	21	87	138	3.6	25	21	YES	YES

Code	K1	TCO21	Cr2	Na2	K2	TCO22	DT	NAC	Vomit
39	3.4	18	71	136	3	22	19	YES	YES
40	4.7	23	71	134	4.6	27	22	YES	YES
41	3.3	24	71	138	3.3	23	22.5	YES	NO
42	3.5	25	62	137	2.6	27	21	YES	YES
43	3.9	22	81	140	3.7	23	22	YES	NO
44	3.6	22	80	138	3.4	24	26	NO	NO
45	2.5	20	78	130	2.4	26	21.5	YES	YES
46	3.6	27	73	141	3.5	30	12	YES	YES
47	3.8	24	88	137	3.8	29	29	YES	NO
48	4.1	26	88	139	3.5	27	19.5	YES	YES
49	4	22	69	139	3.5	27	21	YES	YES
50	4.2	18	64	138	3.3	21	23.5	YES	YES
51	4.4	25	80	137	3	28	20	YES	YES
52	3.8	24	88	137	3.5	23	14	YES	NO
53	3.2	23	69	141	3.6	23	21.5	YES	YES
54	4.1	24	79	139	3.4	26	22.5	YES	YES
55	3.5	26	78	137	3.6	26	23	YES	YES
56	3.4	24	71	137	3.2	25	21	YES	NO
57	3.4	25	106	141	3.3	23	14	NO	YES
58	3.8	23	105	136	3.8	21	21	YES	YES
59	3.8	24	85	140	3.6	26	8	YES	NO
60	3.7	19	72	141	3.3	20	21	YES	YES
61	4.1	22	95	141	4	30	21	YES	YES
62	5.2	28	112	143	3.9	28	22	YES	NO
63	3.7	20	100	138	4.1	23	24	YES	NO
64	3.7	25	96	141	3.8	24	24	YES	YES
65	4	29	75	140	4	29	28	YES	NO
66	3.7	22	85	137	3.4	28	22.5	YES	NO
67	3.8	21	64	141	3.5	23	23.5	YES	YES
68	3.9	23	70	139	3.3	23	27	YES	YES
69	4.3	20	68	139	3.5	21	22	YES	NO
70	3.7	23	73	141	3.3	25	21	YES	YES
71	4.5	20	78	136	3.4	21	22	YES	NO
72	3.9	22	77	138	3.8	23	24	YES	NO
73	3.3	23	72	137	3.4	27	28	YES	NO
74	3.3	23	79	138	3.3	27	22	YES	YES
75	3.3	18	68	137	3	27	23.5	YES	YES
76	3.6	24	80	135	3.3	24	30	YES	YES
77	3.6	23	78	141	3.9	26	5.5	NO	NO
78	3.7	23	102	141	3.9	26	20	NO	YES
79	3.9	19	77	140	3.2	26	19	YES	YES
80	4.4	27	76	140	3.7	26	24	YES	YES
81	4	21	106	138	3.9	25	22	YES	NO
82	3.8	27	84	134	3.2	26	23	YES	YES
83	4.2	23	82	140	3.2	26	22	YES	YES
84	3.8	28	80	135	3.1	29	20	YES	NO
85	4.8	27	76	138	3.8	26	23	YES	NO
86	3.9	28	69	138	3.4	27	23	YES	YES
87	4.1	22	64	136	3.5	23	22	YES	YES
88	3.8	23	72	138	4.4	22	21.5	YES	YES
89	3.5	22	69	139	3.7	24	21.5	YES	YES

Code	K1	TCO21	Cr2	Na2	K2	TCO22	DT	NAC	Vomit
89	3.5	22	69	139	3.7	24	21.5	YES	YES
90	4	21	85	138	3.5	25	28.5	YES	NO
91	3.8	19	85	137	3.6	25	21	YES	NO
92	3.9	25	93	141	3.8	26	.	NO	NO
93	4.1	27	89	141	3.6	22	14	NO	NO
94	3.9	18	76	138	3.1	23	23.5	YES	NO
95	4.1	24	63	137	3.6	22	22	YES	NO
96	4	23	82	138	3.4	22	21.5	YES	YES
97	3.6	20	77	140	3	21	24	YES	YES
98	3.4	27	82	138	3.2	27	29	YES	YES
99	3.9	23	72	138	3.9	24	22.5	YES	NO
100	4	19	84	138	3.1	24	21.5	YES	YES
101	3.5	22	76	139	3.2	24	22.5	YES	YES
102	4.2	25	72	138	3.2	25	24	YES	YES
103	3.7	24	81	140	3.5	26	27	YES	YES
104	2.9	22	66	135	3	27	25	YES	YES
105	4.1	26	81	139	4.1	25	7.5	NO	NO
106	3.9	24	72	141	3.2	29	22	YES	YES
107	4	21	94	139	4.2	28	21	YES	NO
108	4	27	63	141	3.4	25	22	YES	NO
109	4.1	25	71	138	3.3	23	22.5	YES	NO
110	4.1	24	75	138	3.7	24	24	YES	NO
111	3.8	23	69	139	3.8	23	24	YES	NO
112	3.8	25	72	139	3.7	25	20	YES	NO
113	3.8	22	97	136	3.8	24	18	NO	NO
114	3.7	20	82	137	3.7	25	24	YES	YES
115	3.9	22	93	140	3.3	25	21	YES	NO
116	3.9	25	77	140	3.1	25	23	YES	YES
117	4.3	25	93	140	3.6	28	21	YES	NO
118	3.3	13	79	135	3.1	17	19	YES	YES
119	3.6	22	68	136	3.2	23	24.5	YES	YES
120	4	20	76	142	3.3	24	26	YES	YES
121	3.3	22	77	134	3	26	12	YES	YES
122	3.9	22	95	139	4	22	28	NO	NO
123	4	19	73	139	3	28	21	YES	YES
124	3.3	24	81	137	3.2	26	23.5	YES	YES
125	3.4	24	104	139	4.3	26	19	NO	NO
126	4.3	21	68	138	3.4	23	25	YES	NO
127	4.4	21	65	138	3.4	23	24	YES	YES
128	4.1	24	101	142	4	24	22	YES	YES
129	4	26	84	138	3.4	26	22	YES	NO
130	3.6	23	76	137	3.5	21	21	YES	YES
131	4.6	24	80	141	3.2	25	30	YES	YES
132	3.6	30	61	136	3.3	26	22	YES	YES
133	3.6	24	93	141	3.6	.	32	YES	NO
134	4.1	22	62	138	3.9	25	24	NO	NO
135	3.4	23	103	136	3.1	28	33	YES	YES
136	3.8	22	76	140	3	24	20	YES	YES
137	3.8	21	96	138	4.2	24	21.5	YES	YES
138	3.9	24	62	135	3.3	26	23.5	YES	YES
139	4.2	20	84	140	3.5	26	21	YES	NO

Code	K1	TCO21	Cr2	Na2	K2	TCO22	DT	NAC	Vomit
140	3.7	21	69	133	3.5	23	24	NO	NO
141	4.7	19	65	136	3.3	23	26	YES	NO
142	4.3	25	80	135	4.4	24	7	YES	NO
143	4.4	21	62	138	3.7	23	24	YES	NO
144	3.1	25	103	139	3.2	27	20	YES	YES
145	4	29	78	140	3.1	29	23	YES	YES
146	4	29	78	141	3.9	29	38	YES	NO
147	3.7	28	84	140	3.4	29	28	YES	NO
148	3.7	16	75	137	3.2	24	22.5	YES	NO
149	3.8	23	62	140	3.5	27	14	NO	NO
150	4.5	20	78	136	3.4	21	22	YES	NO
151	3.9	23	70	139	3.3	23	22	YES	YES
152	3.7	23	73	141	3.3	25	23	YES	YES
153	4.4	25	79	142	3.7	26	29	YES	YES
154	4.1	21	88	138	3.4	22	21.5	YES	YES
155	4	29	86	140	3.6	31	20	YES	YES

Code: patient code
DOB: date of birth
F: female; M: Male
DOA: date of admission
1: frist sample taken at admission;
2: second sample taken
Cr: plasma Creatinine (µmol/l);
Na: plasma sodium (mmol/l);
K: plasma potassium (mmol/l);
TCO2: plasma bicarbonate (mmol/l),
DT: time between two first and second sample (h),
4h para: plasma paracetamol at 4h post-ingestion (mg/l)
Sali: plasma salicylate

Appendix 2.9: Original data of patients with single paracetamol overdose (Prospective study), n=41.

Code	age y	Sex	tab gr	Risk	Vom_p_inges	NAC	Vom_p_NAC	ST4h	ST12h
1	21.5	F	17	No	Yes	Yes	Yes	4.3	15
2	18.9	F	11.5	No	Yes	Yes	Yes	4	12
3	37.5	F	17	Yes	No	No		5.5	12
4	55	M	10	No	No	No		4	12
5	18.5	M	40	No	No	Yes	Yes	4	12
6	20.5	M	24	No	Yes	No		4	12
7	17.5	F	27.5		Yes	Yes		4	12
8	42.4	F	13.5	No	No	Yes	Yes	4	12
9	37.5	M	13	Yes	No	No		4.5	12
10	22	F	40	No	Yes	Yes	Yes	3.5	11
11	37.6	M	24	Yes	No	Yes	Yes	4.5	13
12	16	F	14	No	Yes	No		4	12
13	34.8	M	26.5	Yes	Yes	Yes	Yes	5	12
14	22	M	18	No	No	No		4	12
15	37.6	F	16	Yes	No	Yes	No	4	12
16	35.9	M	30	Yes	No	Yes	No	4	12
17	21.3	F	15	No	No	Yes	Yes	4	12
18	16.6	F	10	No	No	No	No	4.5	12
19	30.2	M	8	No	No	No	No	4	12
20	22.1	F	20	No	Yes	Yes	Yes	4	12
21	26.3	F	20	Yes	No	Yes	Yes	4	12
22	37.8	M	8	No	No	Yes	No	4.5	12
23	37.7	M	24	Yes	No	Yes	No	4	12
24	43.6	F	16	No	No	Yes	No	4	12
25	19.8	M	12	No	Yes	No		3.5	13
26	57.8	F	7.5	No	Yes	Yes	No	5	12
27	19.5	M	10	No	No	No		4	12
28	18.8	F	25	No	No	Yes	Yes	4	13
29	18.7	M	12	No	Yes	No		4.5	12
30	46.2	M	32	No	No	Yes	Yes	6	12
31	47.4	F	20	No	No	Yes	Yes	4.5	12
32	27.7	F	16	No	Yes	Yes	Yes	4	12
33	37.3	M	24	No	No	No		4	12
34	43.4	F	20	Yes	No	Yes	Yes	4.2	12
35	17.9	F	22	No	No	Yes	No	4	13
36	19.4	F	14.5	No	No	No		4.4	12
37	48.7	F	10	Yes	Yes	No		6.6	14
38	16.4	F	5	No	No	No		4	12
39	19.8	F	4	No	No	No		4	12
40	43.9	F	12	No	No	No		4	12
41	18.2	F	15	No	Yes	Yes	Yes	4.5	15

Code	ST24h	4hpara	K4h	K12h	K24h	FeK4h	FeK12h	FeK24h
1	24	93	3	2.9	3.5	9.1	7.4	6.6
2	26	157	3.9	3.3	3.5	18.4	15.3	4
3	24	75	3.7	3.5		14.7	4.4	
4	24	74	4.2	3.7	3.7	6.4	7.2	7
5	24	285	3.2	3.2	3	24	30.7	6
6	24	50	4	3.9	3.9	10.5		3.7
7	24	89	3.9	3.5	3.4	15.3	13.7	6.7
8	28	137	4.2	4	3.3	8.1	39.5	0.7
9	24	34	4	4.2		13	9.7	
10	24	112	4.1	3.8	3.4	19	15.8	7.8
11	24	129	4.5	4	4.1	18.5		9.4
12	24	44	4.4	4.1		8	7.8	
13	24	115	4.1	3.6	3.4	10.3	22.1	4.9
14	24	80	4.2	3.6		18.6	3.7	
15	26	139	4.1		4.3	16.4		5.2
16	24	159	3.7	4	3.5	40.9	27.5	31
17	24	190	4.2	4.3	3.3	8.8	26	4.6
18	24	61	3.9	3.5	3.7	15	5.8	2.5
19	24	83	3.9	3.9		15.3	14	
20	24	200	4	3.8	3	32	26.6	5
21	24	108	3.9	3.3	4.7	14.7	7.7	4.8
22	24	129	3.5	3	3.9	7.4	24	6.6
23	24	151	3.9	3.3		11.3	40.1	
24	24	177	3.5	3.3	3.7	14.8	11.7	7.9
25	22	99	4.7	4.1	3.9	4.3	11.2	4.3
26	24	140	3.5	.	2.8	48.6		17.1
27	23	127	4.1	3.4	3.4	5.1	15.7	5.5
28	24	216	4	3.2		25.8	31.6	
29	27	116	3.7	3.4	3.8	16.2	16.9	1.9
30	28	270	4		3.5	27.8		7.4
31	23	167	3.5	3.2	3.1	21		7.8
32	24	398	4.3	4.1		9.7	26.6	
33	19	148	4.2	3.7	4.2	17.5	8.5	3.6
34	28	391	3.1	2.9	2.9	4.6	19.5	6.4
35	24	246	3.9	3.6		19.8	19.2	
36	23	137	4	3.9	3.9	9.8	7.8	4.7
37	20	24	3.9	3.5	3.7	23.4	12.6	4.8
38	22	36	3.9	4.2	3.9	8.6	5.3	6.4
39	24	24	3.7		4.8	5.3		4.8
40	25	32	4	3.6	3.8	21.5	9.6	29
41	24	83	3.6	3.8		19.2	14.8	

Code	TTKG4h	TTKG12h	TTKG24h	PO44h	PO412h	PO424h	FePO4h	FePO12h
1	3.20	4.59	3.74	0.76	0.88	0.63	10.6	26.6
2					0.8	1.04		
3	7.55	3.71		1.62	1.46		10.7	22.7
4	5.04	5.47	6.07	0.93	1.22	0.66	5.5	12.6
5	10.49	17.52	6.37	0.87	1.21	1		
6	9.56		2.85	1.52	1.46	0.87	5.3	
7	9.39	10.63	7.23	1.09	1.07	0.74	13.6	25.9
8	4.06	21.24	10.09	1.09	0.96	0.85	10.9	24
9	10.23	5.31			1.4			
10	9.12	8.09	7.44	0.96	0.96	0.92	21.4	12.4
11	10.90		6.96	1.42	1.16	1.08	5	
12	9.02	7.33		1.66	1.6		5.2	18.4
13	8.00	13.09	3.47	1.15	1.26	1.23	13.8	8.8
14	8.16	2.49		1.41	1.41		18	15.1
15	8.59		3.87	1.41		1.12	5.7	
16	11.71	10.93	12	1.17	0.69	0.76	29.3	27.9
17	4.85	12.42	5.98	1.67	1.78	0.91	2.7	17
18	10.10	3.1	3.08	0.93	1.02	0.85	11.8	31
19	10.23	9.12	.	1.57	1.28		31.3	26.2
20	12.84	9.51	4.46	0.96	0.8	0.85	30.8	11.8
21	5.25	4.01	2.92	1.4		1.19	14.1	
22	3.50	14.48	5.84	1.32	0.95	0.74	12.8	18
23	5.91	20.97	.	1.21	1.05		28.3	26.3
24	9.57	5.88	6.96	1.24	1.24	1.22	9	17
25	6.56	10.25	5.4	1.38	1.61	1.17	5.5	16
26	12.67		9.12	1.06		0.42	37.5	
27	5.17	12.75	5.15	0.89	1.23	1.01	5.2	14.3
28	14.82	18.06	.	1.13	1	0.98	18.8	15.3
29	11.47	13.34	2.36	1.07	1.05	0.58	17.5	22.2
30	8.27		4.53	0.8		0.65	43.2	
31	15.14		5.38	0.95	0.72	0.68	16.4	
32	3.92	12.98		0.88	0.91		1.5	26.2
33	10.53	6.17	2.62	1.2	1	0.82	8.6	17.8
34	3.18	10.77	5.44	0.55	1.03	1.35	13.8	25.2
35	13.19	13.85		1.48	1.56		11.8	9.7
36	7.48	6.36	3.86	1.14	1.35	0.72	5.8	20.3
37	20.62	11.05	5.01	1.05	1.11	0.68	45.5	27.6
38	5.98	3.07	3.44	1.48	1.49	1.28	15	12.7
39	3.43		3.37	0.93		0.95	6.9	
40	17.87	7.27	23.57	1.46	1.21	0.97	10.4	15.4
41	13.04	7.98		1.22	0.72		21.4	9.3

Code	FePO424h	CNa12h	CNa24h	FeNa4h	FeNa12h	FeNa24h	CMg12h	CMg24h
1	14.1	0	0	1.66	0.84	1.16	0.05	0.09
2		-2	0	0.60	0.82	0.22		
3		2		0.62	0.34		-0.03	
4	13.8	-2	0	0.37	0.4	0.48	0.04	-0.01
5		0	0	1.17	0.65	0.25	0.18	0.29
6	4.5	1	0	0.17	.	0.33	0.08	0.07
7	24.6	-1	0	0.56	0.38	0.25	0.15	0.06
8	0.7	-1	0	0.16	0.13	0.04	-0.12	-0.1
9		-1		0.22	0.63		-0.01	
10	18.1	2	0	0.57	0.66	0.45	0.04	0.03
11	7.5	-4	0	0.44		0.55	0.03	-0.02
12		2		0.29	0.25		0.05	
13	22.1	0	0	0.50	0.59	0.62	0.02	0.06
14		-1		0.91	0.63		-0.01	
15	6.4		0	0.72		0.58		0
16	25.1	-2	0	2.00	1.57	0.67	-0.04	0
17	4.5	-3	0	0.60	0.54	0.12	0.09	0.04
18	8.6	-1	0	0.49	0.95	0.16	0.1	0.05
19		-3		0.36	0.27		0	
20	14.2	3	0	0.74	1.05	0.17	-0.04	0.12
21	3	1	0	1.68	0.91	0.69	0.01	-0.02
22	14.2	1	0	0.51	0.46	0.36	-0.09	-0.03
23		1		0.85	0.49		0.12	
24	15.9	2	0	0.35	1.03	0.63	0.03	0.05
25	13.7	3	0	0.11	0.13	0.03	0.05	-0.02
26	0.8		0	1.78	.	0.67		0.11
27	6.1	1	0	0.26	0.37	0.22	0.07	0.18
28		-1		0.52	0.56		0.08	
29	1.9	1	0	0.33	0.14	0.01	0.1	0.16
30	28.8		0	1.11		0.23		0.19
31	20.9	-3	0	0.44		0.82	0.04	0.02
32		-2		0.78	0.67		0.03	
33	11.5	1	0	0.32	0.3	0.3	0.02	-0.01
34	14.4	4	0	0.54	0.32	0.06	0.13	0.18
35		-2		0.42	0.36		0.19	
36	19.1	1	0	0.54	0.44	0.38	0.13	0.07
37	19.8	0	0	0.24	0.23	0.1	-0.02	-0.03
38	6.9	-2	0	0.39	0.72	1.03	-0.02	-0.04
39	1.1		0	1.16		0.57		0
40	20.5	-1	0	0.32	0.61	0.27	0	-0.06
41		0		0.57	0.96		-0.03	

Code	FeMg4h	FeMg12h	FeMg24h	Cr4h	Cr12h	Cr24h	Ucr4h	UCr12h
1	6.5	1.5	3.1	68	67	82	8	5.3
2				63	64	64	10.2	10.9
3	1.3	4.1		83	78		3.5	10.5
4	1.1	1.6	1.7	97	90	95	4.7	7.8
5	2.8	0.6	2.4	83	83	86	12	19.1
6	2.7		5	101	90	93	38.5	
7	1			66	61	68	13.8	9
8	4.3	0.6	0	62	66	67	1.1	9.2
9	1.5	3.2		82	76		11.8	5.4
10	2.1	3.9	1.5	78	81	70	1.9	5.8
11	0.7		2.4	77	78	74	15.8	
12	2.1	2.2		78	80		22.2	16.1
13	2.7	0.4	1	87	78	73	21.5	17.8
14	1.8	3		87	85		4.9	17
15	0.8		1.8	78		85	4.4	
16	1.7	1.2	1.1	102	92	91	5.8	11.4
17	3	2.1	1.5	83	85	73	7.6	11.6
18	2.2	3.2	2.9	84	77	90	20.2	1.9
19	1.8	1.2		72	72		9.9	9.9
20	0.8	2.8	2.5	74	75	71	1.1	7.5
21	2.9	4.1	3.4	83	79	84	2.6	6.2
22	4.2	1.3	1.2	78	75	77	1.8	4.9
23	1.5	1		78	84		10.3	11
24	0.6	2.4	2.6	92	86	81	9.4	5.1
25	1.6	0.9	1.5	110	101	97	50.6	34.3
26	9.4	.	2.8	86		102	4.5	
27	1.5	0.9	3.8	85	89	93	6.1	23.2
28	3.3	2.8		79	80	77	1.3	11.4
29	0.6	0.6	2.1	83	93	91	22	26.7
30	1.5		2.5	106		98	10	
31	2.1		3.3	69	64	68	10.6	
32	5	2		79	83	.	5.5	12.5
33	2.3	3.6	6.9	88	89	95	14.4	24
34	2	0.5	2	80	80	81	11.2	4.1
35	1.5	1.1		75	70	.	13.5	13.9
36	1.7	2.6	3.3	82	82	74	6.7	13.7
37	1.6	0.8	2.9	64	63	61	11.7	9.7
38	3.5	5.5	4.4	69	70	69	8.2	6.2
39	2.4		3	74		78	11.8	
40	2	2.6	0.5	83	72	74	10.7	11.8
41	2.4	4.6	.	66	70		8.3	4.6

Code	UCr24h	CTOC2-12h	CTCO2-24h	U/Posom12h	U/Posom4h	U/Posmo24h
1	5.7	2	1	1.28	3.33	1.22
2	5.1	-3	1	2.81		0.92
3		-2		1.62	0.82	
4	7.3	-2	-2	1.14	0.61	0.89
5	25.4	-1	1	4.03	3.31	2.77
6	14.2	2	0		4.19	1.98
7	15.1	3	3	1.91	3.41	2.08
8	67	1	3	2.59	0.35	0.6
9		3		1.3	1.83	0
10	4.2	0	0	1.4	0.51	0.63
11	8.4	-2	1		3.49	1.54
12	0	1		2.13	2.52	
13	17.5	-2	-1	3.84	3.17	3.39
14		1		3.01	1.28	0
15	9		3		1.08	1.44
16	5.9		-4	3.11	1.99	1.04
17	9.6	0	2	2.87	1.67	1.01
18	8.8	-2	-3	0.46	3.58	0.79
19		2		2.11	2.05	
20	7.2	0	0	2.79	0.37	1.12
21	3.3	-1	1	1.51	0.88	0.65
22	10.8	5	3	1.08	0.49	1.58
23		3		2.5	2.52	
24	13	2	2	1.18	1.58	1.83
25	32.6	8	9	3.71	3.05	2.71
26	3.2		-1		2.01	0.59
27	18	-3	1	3.21	0.71	2.06
28		2		2.49	0.29	0
29	25.9	-4	3	3.64	3.75	2.34
30	12.5		1		3.17	2.08
31	3.1	0	1	0	2.13	0.66
32	.	0		3.08	1.72	
33	23.9	-1	0	3.68	2.71	3.45
34	8.7	0	2	0.93	2.03	1.27
35		-1		2.75	2.7	
36	5.7	3	2	2.06	1.07	0.93
37	16.2	-1	2	1.76	2.08	2.54
38	6.3	-1	1	1.55	1.71	1.72
39	7.8		2		2.44	1.42
40	14.2	1	5	2.18	1.55	2.37
41		2		1.22	1.85	

Risk: high risk; Vom_P_inges: vomiting post ingestion; Vom_P_NAc: vomiting post NAC infusion; ST4h: time of 4h sample taken (h); ST12h: time of 12h sample taken (h); ST24h: time of 24h sample taken (h); 4hpara: paracetamol level at 4h (mg/l); K4h: plasma potassium at 4h (mmol/l); K12h: plasma potassium at 12h; K24h: plasma potassium at 24h; FeK4h: FeK at 4h (%); Fe12h: FeK at 12h; Fe24h: FeK at 24h; TTKG4h: TKG at 4h; TTKG12h: TTKG at 12h; TKG24h: TTKG at 24h; PO44h: plasma phosphate at 4h (mmol/l); PO412h: plasma phosphate at 12h; PO424h: plasma phosphate at 24h; FePO4h: FePO4 at 4h (%); FePO12h: FePO4 at 12h; FePO24h; FePO4 at 24h; CNa12h:cange in plasma sodium at 12h (mmol/l); CNa24h: change in plasma sodium at 24h; FeNa4h: FeNa at 4h (%); FeNa12h: FeNa at 12h; FeNa24h: FeNa at 24h; CMag12h: Change in plasma magnesium at 12h (mmol/l); CMg24h: Change in plasma magnesium at 24h; FeMg4h: FeMg at 4h (%); FeMg12h: FeMg at 12h; FeMg24h: FeMg at 24h; Cr4h: plasma Creatinne (Cr) at 4h (µmol/l); Cr12h: plasma Cr at 12h; Cr24h: plasma Cr at 24h; UCr4h: urine Cr at 4h (mmol/l), UCr12h: urine Cr at 12h; UCr24h: urine Cr at 24h; CTCO2-12h: change in plasma bicarbonate at 12h (mmol/l); CTCO2-24h: change in plasma bicarbonate at 24h; U/Posmo12h: urinary osmolality/plasma osmolality at 12h; U/Posmo24h: urinary osmolality/plasma osmolality at 24h;

Appendix 2.10: Original data of patients with single SSTI (Fluoxetine) overdose (Prospective study), n=18.

Code	age y	Sex	tablet gr	Vom_Pingestion	T4h	T12h	T24h	4hpara
1	28	M	0.48	No	4	12	.	0
2	27	M	0.46	No	3.5	12	24	0
3	21	F	0.6	No	4	12	20	0
4	43.8	F	0.4	No	5	12	.	0
5	25.7	M	0.4	No	5	12	24	0
6	54.5	F	2	Yes	6	12	0	0
7	19.6	F	0.4	Yes	4	12	.	0
8	37.1	M	0.44	Yes	6	12	.	0
9	22.9	F	0.84	Yes	4	12	24	0
10	24.3	F	0.42	No	4	12	21	0
11	17	F	1.2	Yes	6	12	24	0
12	45.8	F	0.9	Yes	4	12	20	0
13	16.2	M	0.6	No	7	10	.	0
14	19.2	M	0.52	No	4	13	20	0
15	20.4	F	0.18	Yes	7	12	22	0
16	27.2	F	3.6	No	2.5	12	.	0
17	41.6	M	6	No	7	16	.	17
18	23.3	F	0.88	Yes	4	12	17	0

Code	cK12h	cK24h	FeK4h	cFeK12h	cFeK24h	TTKG4h	cTTKG12h	cTTKG24h
1	-0.2		8.2	0.03		4.96	4.98	
2	-0.1	0.6	31	-0.07	-0.14	0.00	13.14	
3	-1	-1.2	7.1	0.00	-0.04	5.34	0.00	-1.39
4	-0.4		8.9	-0.04		5.27	-0.86	
5	-0.1	-0.4	5.7	0.06	-0.01	4.34	2.72	-1.18
6	0		9.6	0.11		7.59	8.14	
7	0.1		4	-0.01		2.40	0.48	
8	0		14.2	0.12		11.26	5.29	
9	-0.5	0	6.6	-0.01		8.20	-2.17	
10	0	0	7.7		0.02	3.04		2.33
11	0.1	-0.1	3.7	0.02	-0.01	3.80	2.29	0.59
12	0.5	0.6	8.6	0.02	-0.01	13.26	-4.17	-6.06
13	0.5		7.7	0.06		4.64	3.83	
14	0.3	0.5	6.8	-0.03	0.01	3.57	0.16	1.96
15	-0.1	-0.5	6.6	-0.01	-0.03	3.85	-0.01	-0.50
16	-0.1		7.8	0.03		7.34	1.86	
17	-0.2		9.6	0.08		7.46	4.25	
18	-0.1	0	3.6	0.03	0.06	2.01	5.79	9.30

Code	PO44h	cPO412h	cPO424h	FePO44h	4hPO4	cFePO12h	cFePO424h
1	1.03	-0.12		3.3	1.03	0.09	
2	1.11	0.23	0.14	14.2	1.11	0.10	0.22
3	0.83		-0.21	8.4	0.83		-0.05
4	0.88	0.31		14	0.88	0.06	
5	1.65	-0.31	-0.3	13.4	1.65	0.06	0.09
6	1.02	-0.17		30.3	1.02	-0.03	
7	1.14	-1.14		12.3	1.14		
8	1.08	0.05		18.6	1.08	0.18	
9	1.25	0.15	-1.25	5.8	1.25	0.03	
10	1.11	0.01	-0.02	21	1.11		-0.05
11	0.95	0.23	0.09	0.7	0.95	0.04	0.00
12	0.88	0.51	0.33	10.1	0.88	0.10	0.07
13	1.46	-0.15		12.9	1.46	-0.01	
14	1.19	-0.05	-0.37	7.4	1.19	0.18	0.05
15	0.92	0.12	-0.08	34.6	0.92	-0.10	-0.09
16	1.08	-0.03		10.4	1.08	0.04	
17	1.22	-0.11		27	1.22	-0.09	
18	0.86	0.39	0.02	4		0.10	0.14

Code	CNa12h	CNa24h	FeNa4h	cFeNa12h	cFeNa24h	CMg12h	CMg24h	FeMg4h
1	-1		0.60	-0.005		-0.03	.	1.8
2	-2	-6	0.80	0.000	-0.003	-0.07	-0.05	3.7
3	2	-1	0.40	0.004	-0.001	0.09	0.1	1.4
4	2		0.70	-0.004		0.01	.	3.7
5	1	-5	0.60	0.002	-0.002	-0.07	0.03	3.1
6	0		0.40	0.001		-0.01	.	2.7
7	-2		1.00	-0.005		-0.02	.	3.8
8	-2		0.60	0.000		-0.02	.	3.4
9	-2	-3	0.20	0.000		-0.07	0.01	1
10	0	-1	1.60		-0.007	-0.01	0.03	3.2
11	0	-1	0.30	0.002	0.000	-0.01	0.02	2.9
12	2	5	0.00	0.003	0.002	0.07	0.07	2.1
13	5		0.70	0.001		0.03	.	2.6
14	2	0	0.40	-0.003	0.001	-0.02	0.02	5.4
15	0	2	0.60	-0.003	-0.004	0.06	0	2.2
16	3		0.50	0.000		-0.03	.	1.9
17	-4		0.40	0.000		-0.06	.	3
18	4	3	0.50	-0.002	-0.001	-0.04	-0.05	7.8

Code	cFeMg12h	cFeMg24h	cCr12h	cCr24h	CTOC2-12h	CTCO2-24h
1	-0.005		1		-1	.
2	-0.019	-0.026	-6	-4	2	1
3	0.007	0.016	0	5	3	1
4	0.007		-1		0	.
5	-0.014	-0.012	15	2	0	.
6	-0.017		3		3	.
7	-0.004		2		-3	.
8	-0.029		-2		1	.
9	0.010		-6		1	2
10		-0.013	3	6	0	-1
11	-0.014	-0.004	-7	-1	-1	-1
12	-0.012	-0.010	-9	-6	2	-1
13	0.000		7		-4	.
14	-0.029	-0.037	7	3	2	2
15	-0.005	0.012	2	7	3	5
16	-0.007		3		6	.
17	-0.004		7		-1	.
18	-0.069	-0.074	6	8	1	4

Code	U/Posom12h	U/Posom4h	U/Posmo24h
1	3.81	2.47	.
2	2.36	.	2.89
3	1.4	1.87	3.31
4	2.84	2.42	.
5	2.58	1.96	3.08
6	2.57	0.94	.
7	4.01	3.4	.
8	2.85	2.1	.
9	3.55	3.29	.
10	.	1.29	2.82
11	0.95	0.29	3.42
12	2.96	2.44	3.26
13	1.82	0.74	.
14	3.96	2.65	3.83
15	3.33	3.3	3.32
16	2.26	1.9	.
17	2.97	1.25	.
18	0.74	0.36	2.29

cK12: change in plasma potassium at 12h (mmol/l); cK24h: change in plasma potassium at 24h; cFeK12h: change in FeK at 12h (%); cFeK24h: change in FeK at 24h; cTTKG12h: change in TTKG at 12h; cTTKG24h: change in TTKG at 24h; cPO412h: change in plasma phosphate at 12h (mmol/l); cPO424h: change in plasma phosphate at 24h; cFePO412h: change in FePO4 at 12h (%); cFePO424h: change in FePO4 at 24h; cNa12h: change in plasma sodoium at 12h (mmol/l); cNa24h: change in plasma sodium at 24h; cFeNa12h: change in FeNa at 12h (%); cFena24h: change in FeNa at 24h; cMg12h: change in plasma magnesium at12h (mmol/l); cMg24h: change in plasma magnesium at 24h; cFeMag12h: change in FeMg at 12h (%); cFeMg24h: change in FeMag at 24h; cCr12h: change in plasma Cr at 12h (µmol/l); cCr24h: change in plasma Cr at 24h;

Appendix 3.1: Collected data from 522 patients admitted to Scottish Liver Transplant Unit from referring hospital in Scotland.

Number	Code	DOB	Sex	Age	Age band	No Tablet	Stag OD
1	TA040001	24-Jun-79	female	16	11-20 YEARS	50	NO
2	DA090002	23-Jun-52	male	47	41-50 YEARS	12	YES
3	IA020004	15-Jan-56	female	36	31-40 YEARS		NO
4	DA070006	24-Apr-62	male	36	51-60 YEARS	32	NO
5	PA030007	15-Oct-65	male	28	21-30 YEARS	40	NO
6	JA080009	30-Dec-75	female	23	21-30 YEARS	40	NO
7	SA080010	30-Mar-65	female	33	31-40 YEARS		YES
8	CA050012	13-Jul-60	female	35	31-40 YEARS	50	NO
9	RA060014	25-Nov-45	male	51	51-60 YEARS	100	NO
10	DA120687	12-Dec-61	female	43	41-50 YEARS		NO
11	DA030015	31-Dec-67	female	26	21-30 YEARS	20	NO
12	AA050016	01-Sep-68	male	28	21-30 YEARS	72	NO
13	CA070017	06-Jun-76	female	22	21-30 YEARS	15	NO
14	EA060019	30-Mar-35	female	61	61 AND OLDER	40	NO
15	AA030021	14-Mar-69	male	25	21-30 YEARS	220	NO
16	JA060023	12-Sep-30	male	66	61 AND OLDER		NO
17	DB020024	05-Nov-55	female	39	31-40 YEARS	18	NO
18	JB060026	16-Jun-48	male	50	41-50 YEARS	100	YES
19	JB120685	21-May-76	female	27	21-30 YEARS	60	YES
20	SB100028	29-Feb-60	female	41	41-50 YEARS	80	NO
21	KB110029	14-Sep-53	female	48	41-50 YEARS		YES
22	MB070030	14-Dec-58	male	39	31-40 YEARS	125	NO
23	MB050032	13-Dec-56	female	39	31-40 YEARS	50	NO
24	VB120681	12-Jul-62	female	42	41-50 YEARS	35	YES
25	DB060034	17-Dec-61	male	35	31-40 YEARS	44	
26	SB040037	27-Nov-65	male	29	21-30 YEARS	60	NO
27	WB060038	02-Jul-60	male	36	31-40 YEARS	48	NO
28	LB110039	21-Sep-82	female	19	11-20 YEARS	64	NO
29	AB120682	23-Dec-50	male	53	51-60 YEARS	112	YES
30	MB050040	21-Jan-51	female	46	41-50 YEARS	100	NO
31	JB070041	14-Mar-55	male	43	41-50 YEARS	75	NO
32	EB060042	09-Feb-74	female	23	21-30 YEARS	50	NO
33	IB060043	10-Feb-57	male	40	31-40 YEARS	150	NO
34	RB040045	11-Feb-43	male	52	51-60 YEARS		YES
35	SB090046	25-Apr-76	female	24	21-30 YEARS	14	YES
36	AB050047	19-Feb-71	female	25	21-30 YEARS	48	YES
37	NB100048	07-Jun-64	male	37	31-40 YEARS	46	NO
38	AB070050	05-Mar-77	male	20	11-20 YEARS	42	NO
39	AB010051	12-Apr-42	male	50	41-50 YEARS	80	NO
40	GB120662	16-Aug-48	female	43	41-50 YEARS	95	NO
41	CB040053	03-Mar-58	female	36	31-40 YEARS	37	
42	AB060055	04-Feb-43	male	54	51-60 YEARS		
43	LB060056	12-Sep-67	female	29	21-30 YEARS	60	NO
44	KB050057	08-Jan-50	male	46	41-50 YEARS	50	NO
45	HB070058	11-Nov-77	female	22	21-30 YEARS	40	NO
46	JB120680	24-Jun-86	female	17	11-20 YEARS	35	NO
47	FB020059	12-Feb-51	female	41	41-50 YEARS	30	NO

Number	Code	DOB	Sex	Age	Age band	No Tablet	Stag OD
48	NB080060	24-Jun-48	female	50	41-50 YEARS		YES
49	JB090062	13-Feb-77	male	23	21-30 YEARS	104	YES
50	JB050063	20-Jun-74	male	22	21-30 YEARS		YES
51	LB060064	25-Feb-68	female	29	21-30 YEARS	72	NO
52	GB110066	01-Feb-40	male	52	51-60 YEARS	50	NO
53	MB060067	01-Oct-75	male	21	21-30 YEARS	50	NO
54	SB100068	17-Jul-66	female	34	31-40 YEARS	64	NO
55	VB080069	11-Jul-63	male	35	31-40 YEARS		
56	MB100070	02-May-77	male	24	21-30 YEARS		NO
57	AB020071	16-Jun-42	male	50	41-50 YEARS	50	YES
58	MB130705	27-Dec-78	male	25	21-30 YEARS	70	NO
59	SB090073	16-Sep-77	female	22	21-30 YEARS	60	NO
60	MB030075	03-Jan-71	female	23	21-30 YEARS	50	NO
61	MB030076	03-Jan-71	female	23	21-30 YEARS	80	NO
62	RB070079	11-Sep-65	female	33	31-40 YEARS	40	NO
63	JB050080	02-Jul-57	male	39	31-40 YEARS	128	
64	RB090081	19-Apr-74	male	26	21-30 YEARS	116	NO
65	PB040082	02-Jul-61	male	34	31-40 YEARS	150	NO
66	MB050083	04-Nov-53	female	40	31-40 YEARS	60	NO
67	SB080085	19-Oct-71	male	27	21-30 YEARS	50	NO
68	GB110086	16-Sep-67	male	34	31-40 YEARS		YES
69	IB050088	24-Oct-45	male	50	41-50 YEARS	40	NO
70	CC060089	24-Jun-62	male	34	31-40 YEARS	50	NO
71	JC040092	30-Oct-74	male	22	21-30 YEARS	50	YES
72	LC050094	22-May-68	female	28	21-30 YEARS	77	NO
73	PC090095	09-Feb-65	male	35	31-40 YEARS	32	NO
74	PC100096	09-Jul-63	female	38	31-40 YEARS	189	NO
75	SC070098	01-Jun-69	female	29	21-30 YEARS	48	NO
76	SC060100	26-Apr-67	male	30	21-30 YEARS	74	NO
77	EC110102	01-Sep-72	female	29	21-30 YEARS	30	NO
78	MC060103	25-Jun-60	male	37	31-40 YEARS	8	NO
79	JC100105	22-May-82	male	18	11-20 YEARS	40	NO
80	MC020108	30-Nov-59	female	34	31-40 YEARS	60	NO
81	HC070109	18-Sep-62	female	35	31-40 YEARS	85	NO
82	VC120683	03-Jun-80	female	23	21-30 YEARS	32	NO
83	JC100113	24-Oct-75	female	25	21-30 YEARS	100	NO
84	AC110114	09-May-76	female	52	21-30 YEARS	64	NO
85	AC080115	13-Jun-65	female	34	31-40 YEARS	55	NO
86	DC110116	03-Nov-75	female	26	21-30 YEARS	23	YES
87	JC120674	28-Oct-55	male	48	41-50 YEARS	50	NO
88	LC070117	29-Jul-68	female	30	21-30 YEARS	30	NO
89	MC040118	03-Jul-61	female	34	31-40 YEARS	50	NO
90	JC110119	08-Nov-65	male	36	31-40 YEARS	40	NO
91	DC070120	14-Sep-41	male	56	51-60 YEARS	45	NO
92	AC17711	07-Aug-71	male	33	31-40 YEARS	100	YES
93	JC040121	18-Sep-58	male	37	31-40 YEARS	25	NO
94	AC070122	17-Mar-66	male	32	31-40 YEARS	25	NO
95	DC070123	11-Oct-60	male	38	31-40 YEARS	60	NO
96	WC110124	19-Aug-39	female	63	61 AND OLDER		UNKNOWN
97	JC110125	03-Dec-50	male	21	51-60 YEARS		YES
98	GC100126	10-Sep-66	male	34	31-40 YEARS	35	NO

Number	Code	DOB	Sex	Age	Age band	No Tablet	Stag OD
149	GC050194	04-Jul-68	male	46	41-50 YEARS	80	YES
99	HC060127	15-Nov-63	male	33	31-40 YEARS	48	NO
100	GC070129	12-Aug-57	male	40	31-40 YEARS	34	YES
101	CC050131	15-Aug-47	female	49	41-50 YEARS	40	
102	WC080132	29-Oct-72	male	26	21-30 YEARS	130	NO
103	AC120135	27-Aug-38	female	65	61 AND OLDER	90	NO
104	LC040136	06-Nov-71	female	23	21-30 YEARS		NO
105	AC090137	24-Apr-78	female	21	21-30 YEARS		YES
106	JC120138	05-Mar-49	male	54	51-60 YEARS	100	NO
107	RC100140	23-Sep-47	male	53	51-60 YEARS	50	NO
108	CC110141	13-Sep-46	male	55	51-60 YEARS		YES
109	PC040142	30-Jul-74	male	20	11-20 YEARS		YES
110	PC130708	18-Jan-72	male	32	31-40 YEARS		YES
111	SC100144	29-Jan-60	female	40	31-40 YEARS	70	NO
112	FC100145	23-Apr-68	female	33	11-20 YEARS		UNKNOWN
113	JC130689	31-Dec-58	male	42	41-50 YEARS	24	NO
114	MC020146	10-Aug-30	female	63	61 AND OLDER		
115	MD120147	27-Feb-73	male	30	21-30 YEARS	22	NO
116	JD020150	29-Aug-51	male	35	31-40 YEARS	50	NO
117	PD030151	17-May-62	female	31	31-40 YEARS	30	NO
118	MD020153	17-Mar-39	female	54	51-60 YEARS	100	NO
119	FD110154	30-Nov-58	male	41	41-50 YEARS	128	NO
120	GD050157	30-Aug-72	male	25	21-30 YEARS	120	NO
121	HD070158	24-Mar-74	female	24	21-30 YEARS	38	NO
122	DD100159	11-Jun-68	male	33	31-40 YEARS	16	YES
123	LD080160	11-Dec-57	female	41	41-50 YEARS	50	NO
124	MD050161	07-Feb-50	female	45	41-50 YEARS		YES
125	RD080162	03-Mar-73	male	26	21-30 YEARS		YES
126	AD050163	08-Jun-52	female	44	41-50 YEARS	100	NO
127	JD080164	30-Jun-56	male	43	41-50 YEARS	50	YES
128	PD120168	11-Sep-59	male	43	41-50 YEARS	40	NO
129	SD040169	15-Jul-73	female	22	21-30 YEARS	50	NO
130	RD050170	30-May-41	female	54	51-60 YEARS		NO
131	VD080171	17-Mar-38	female	61	61 AND OLDER	14	YES
132	SD040174	03-Jul-76	male	19	11-20 YEARS	50	NO
133	SD050175	18-Dec-56	female	39	31-40 YEARS	58	NO
134	MD040176	16-Jun-30	female	64	61 AND OLDER	140	NO
135	AD090177	09-Mar-58	male	42	41-50 YEARS	90	YES
136	PD060178	05-Dec-52	female	44	41-50 YEARS		YES
137	AD060179	09-Aug-46	female	50	41-50 YEARS		
138	DD120180	21-Nov-50	male	52	51-60 YEARS	160	NO
139	PD120181	27-Aug-79	male	22	21-30 YEARS		YES
140	JE130709	17-Apr-68	male	36	31-40 YEARS		NO
141	IE050185	20-Jul-53	male	44	41-50 YEARS	200	NO
142	BE120187	31-Mar-75	female	28	21-30 YEARS	20	YES
143	RE060188	25-Apr-37	male	59	51-60 YEARS	40	NO
144	FF060189	15-Dec-71	female	25	21-30 YEARS	50	NO
145	TF040190	29-Oct-70	female	24	21-30 YEARS	48	NO
146	HF120191	16-May-53	female	50	41-50 YEARS		UNKNOWN
147	CF020192	11-Apr-37	male	56	51-60 YEARS		YES
148	GF100193	14-Jan-47	female	54	51-60 YEARS	92	NO

Number	Code	DOB	Sex	Age	Age band	No Tablet	Stag OD
149	GF050194	14-Jul-68	male	28	21-30 YEARS	36	YES
150	NF060197	01-May-59	male	38	31-40 YEARS	120	NO
151	RF030198	16-Sep-66	male	28	21-30 YEARS		YES
152	SF030202	24-Sep-73	female	20	11-20 YEARS	30	NO
153	AF090203	23-Mar-62	female	38	31-40 YEARS	50	NO
154	MF130704	27-Nov-38	female	65	61 AND OLDER		UNKNOWN
155	EF080205	12-Nov-57	female	41	41-50 YEARS	42	NO
156	YF09207	29-Aug-63	female	37	31-40 YEARS		UNKNOWN
157	JF09208	25-Mar-51	male	47	41-50 YEARS	170	NO
158	JF070210	12-Nov-47	male	50	41-50 YEARS	150	NO
159	AF060211	03-Feb-70	female	27	21-30 YEARS	50	NO
160	AF050213	13-Jul-29	female	66	61 AND OLDER		
161	EF060218	21-May-56	male	41	41-50 YEARS	75	NO
162	KF050219	21-Jun-66	male	30	21-30 YEARS	90	NO
163	AF100220	26-Mar-56	male	45	41-50 YEARS	80	YES
164	DF090222	16-Feb-71	female	29	21-30 YEARS		YES
165	RG050224	22-Dec-76	male	19	11-20 YEARS	300	NO
166	SG050225	16-Sep-66	male	30	21-30 YEARS	54	NO
167	CG100226	22-Feb-32	male	69	61 AND OLDER	89	NO
168	LG110227	11-Jul-80	female	21	21-30 YEARS	48	NO
169	NG040228	04-Aug-74	female	20	11-20 YEARS	20	NO
170	SG020230	14-Jul-71	male	22	21-30 YEARS	17	NO
171	CG130707	26-May-71	male	33	31-40 YEARS	130	YES
172	JG020231	05-Jun-55	male	38	31-40 YEARS	100	NO
173	LG100232	13-Mar-72	male	29	21-30 YEARS	60	YES
174	AG110234	30-Jun-55	male	46	41-50 YEARS		YES
175	MG030236	15-Apr-58	female	36	31-40 YEARS	50	NO
176	SG100237	04-Feb-82	male	29	21-30 YEARS	50	NO
177	MG030239	17-Sep-76	female	17	11-20 YEARS	40	NO
178	AG100242	17-Oct-59	male	41	41-50 YEARS	40	YES
179	AG030243	25-Sep-71	female	22	21-30 YEARS	24	NO
180	DG090244	11-Dec-76	male	23	21-30 YEARS	100	NO
181	SG080245	29-Oct-68	female	30	21-30 YEARS		NO
182	SG080248	03-Feb-75	female	23	21-30 YEARS	50	NO
183	SG060249	27-Sep-81	female	16	11-20 YEARS	38	NO
184	CG120251	20-Oct-65	female	37	31-40 YEARS		UNKNOWN
185	DG120252	26-Aug-72	female	30	21-30 YEARS	20	NO
186	FG100253	24-May-74	female	27	21-30 YEARS	40	NO
187	SG040254	13-Dec-69	female	26	21-30 YEARS	50	NO
188	LG080255	15-Oct-68	female	31	31-40 YEARS	32	YES
189	PG040256	24-Jul-71	male	23	21-30 YEARS	70	NO
190	SG090260	21-Mar-69	female	31	31-40 YEARS	90	YES
191	JH050263	06-Feb-47	female	49	41-50 YEARS	72	NO
192	RH120264	15-Feb-44	male	59	51-60 YEARS		YES
193	IH020265	11-Mar-74	female	19	11-20 YEARS		NO
194	AH010268	16-Sep-70	male	22	21-30 YEARS		YES
195	MH060269	12-Feb-80	female	17	11-20 YEARS	70	NO
196	WH020271	10-Sep-44	male	48	41-50 YEARS	50	NO
197	JF030273	21-Oct-64	female	29	21-30 YEARS	30	NO
198	JH080274	30-Sep-37	male	62	61 AND OLDER		YES

Number	Code	DOB	Sex	Age	Age band	No Tablet	Stag OD
199	KH030275	19-Mar-45	male	48	41-50 YEARS	250	NO
200	RH060276	09-Jan-55	male	42	41-50 YEARS	60	NO
201	PH110277	19-Sep-62	female	39	31-40 YEARS		YES
202	BH090279	29-Jun-71	female	29	21-30 YEARS	100	NO
203	JH070280	10-Apr-72	male	26	21-30 YEARS	60	NO
204	PH060281	10-Dec-44	male	53	51-60 YEARS	40	NO
205	LH120282	20-Oct-60	female	42	41-50 YEARS	32	NO
206	KH060283	02-Apr-80	female	17	11-20 YEARS	40	NO
207	AH040284	22-Jun-74	female	21	21-30 YEARS	48	NO
208	VH060286	08-Sep-79	female	18	11-20 YEARS	14	NO
209	KH090287	08-Dec-67	male	32	31-40 YEARS	50	NO
210	AH050288	20-Jan-72	female	24	21-30 YEARS	60	NO
211	LH070289	22-Jan-77	female	21	21-30 YEARS	48	NO
212	BH080290	05-Jan-82	male	17	11-20 YEARS		UNKNOWN
213	CH090291	07-Oct-55	female	45	41-50 YEARS	48	YES
214	SH130692	24-Aug-60	male	43	41-50 YEARS	100	NO
215	LH030293	18-Sep-62	female	31	31-40 YEARS	35	
216	TH070294	10-Feb-40	male	58	41-50 YEARS	72	YES
217	TI060296	25-Dec-68	female	28	21-30 YEARS	70	NO
218	JI040297	09-Jun-79	female	16	11-20 YEARS	40	NO
219	LI120355	14-Mar-74	female	28	21-30 YEARS	100	NO
220	RI120298	24-Mar-54	female	47	41-50 YEARS	60	NO
221	FI050300	10-Mar-63	male	32	31-40 YEARS	100	NO
222	JJ080302	27-May-43	male	56	41-50 YEARS	40	YES
223	MJ100303	10-Apr-44	female	57	51-60 YEARS	56	NO
224	BJ090304	03-Apr-55	male	45	31-40 YEARS	80	YES
225	AJ090305	20-Dec-67	male	32	31-40 YEARS	10	YES
226	WJ030306	27-Jun-49	male	44	41-50 YEARS	100	YES
227	AJ050307	09-Aug-75	female	20	11-20 YEARS	60	NO
228	BJ040308	08-Nov-76	female	18	11-20 YEARS	16	NO
229	AJ100309	09-Nov-62	female	38	31-40 YEARS	196	NO
230	EJ080310	05-Apr-43	female	56	51-60 YEARS	70	UNKNOWN
231	SJ010311	28-Feb-63	female	29	21-30 YEARS		UNKNOWN
232	PJ110312	06-Jun-69	male	33	31-40 YEARS		YES
233	TK120313	17-Mar-76	male	23	21-30 YEARS	50	NO
234	BK050314	16-Jul-65	male	30	21-30 YEARS	100	NO
235	JK100316	16-Jul-61	male	40	31-40 YEARS	32	NO
236	KK060317	28-Jan-81	female	16	11-20 YEARS	32	NO
237	MK090318	24-Nov-76	female	24	21-30 YEARS	38	YES
238	RK090320	08-Mar-47	male	52	51-60 YEARS	50	NO
239	WK060321	24-Apr-52	male	44	41-50 YEARS	100	NO
240	LK040323	22-Mar-61	female	34	31-40 YEARS	10	NO
241	WK130700	29-Aug-29	male	74	61 AND OLDER	96	NO
242	GK120327	18-Dec-45	male	57	51-60 YEARS	60	NO
243	JK020330	27-Oct-59	female	34	31-40 YEARS	20	NO
244	TK050331	14-Dec-71	male	24	21-30 YEARS	200	NO
245	SK100333	16-Aug-76	male	25	21-30 YEARS	72	YES
246	JK120334	08-Dec-73	male	29	21-30 YEARS	100	NO
247	LL060335	26-Mar-60	female	36	31-40 YEARS		UNKNOWN
248	FL120336	28-Nov-64	female	38	31-40 YEARS		YES

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249	FL090338	06-Oct-66	female	34	31-40 YEARS		UNKNOWN
250	KL050339	08-Jul-74	female	22	21-30 YEARS	18	NO
251	SL050340	21-Apr-81	female	14	11-20 YEARS	35	NO
252	DL070341	27-Feb-74	male	24	21-30 YEARS	93	NO
253	JL120676	29-Aug-24	female	79	61 AND OLDER		UNKNOWN
254	LS050343	15-Oct-44	male	50	41-50 YEARS	70	NO
255	JL090344	03-Oct-50	male	49	41-50 YEARS		NO
256	AL030345	08-Mar-65	female	29	21-30 YEARS	35	NO
257	JL030347	18-Dec-67	female	26	21-30 YEARS	30	NO
258	WL040348	21-Sep-60	male	34	31-40 YEARS	100	NO
259	DL070349	20-Mar-22	female	76	61 AND OLDER		
260	SL050351	27-Mar-75	female	21	21-30 YEARS	20	NO
261	KL120352	07-Jul-73	female	30	21-30 YEARS	60	NO
262	LL040353	17-May-79	female	16	11-20 YEARS	80	NO
263	EL030354	13-Jan-33	male	61	61 AND OLDER		NO
264	CL030356	08-Jul-57	female	37	31-40 YEARS	50	NO
265	RL050367	17-Aug-74	male	22	21-30 YEARS		UNKNOWN
266	SM120594	04-Nov-76	male	26	21-30 YEARS	70	NO
267	DM080358	27-May-99	male	55	41-50 YEARS	12	YES
268	CM080359	23-Jul-55	female	44	41-50 YEARS		
269	KM030360	21-Jun-69	female	25	21-30 YEARS	50	NO
270	FM030361	19-Jul-60	female	33	31-40 YEARS	42	YES
271	RM070362	28-Apr-53	female	44	41-50 YEARS		YES
272	SM120363	07-Aug-74	female	27	21-30 YEARS	32	NO
273	LM100364	25-Oct-79	female	22	21-30 YEARS	170	NO
274	JM030367	14-May-57	female	38	31-40 YEARS		YES
275	VM080368	18-Sep-71	female	27	21-30 YEARS	96	NO
276	WM080369	28-Jul-38	male	60	51-60 YEARS	100	NO
277	WM040370	12-Jul-54	male	40	31-40 YEARS		NO
278	KM100371	31-Oct-77	female	23	21-30 YEARS		YES
279	CM090372	02-Apr-75	female	23	11-20 YEARS	96	YES
280	BM100374	01-Nov-73	male	28	21-30 YEARS	16	YES
281	SM030375	24-Aug-82	female	11	11-20 YEARS	20	NO
282	CM060377	02-Apr-76	male	21	21-30 YEARS	27	NO
283	SM060378	06-Oct-64	male	32	31-40 YEARS		NO
284	SM040379	21-Jul-64	female	30	21-30 YEARS	130	NO
285	UM040380	17-May-53	female	41	41-50 YEARS		YES
286	WM040382	09-Jul-50	male	45	41-50 YEARS	200	NO
287	AM100383	01-Feb-29	male	71	61 AND OLDER		UNKNOWN
288	JM110384	15-Oct-62	male	39	21-30 YEARS		UNKNOWN
289	AM070385	19-Aug-75	female	22	21-30 YEARS		NO
290	CM110386	23-Dec-63	female	38	31-40 YEARS	60	NO
291	JM110387	23-Oct-35	male	66	61 AND OLDER	85	NO
292	SM130693	27-Dec-65	male	38	31-40 YEARS	130	YES
293	KM050389	15-Dec-56	female	39	31-40 YEARS		YES
294	TM120678	11-Oct-28	male	75	61 AND OLDER		YES
295	EM060390	29-Jun-50	female	47	41-50 YEARS		
296	KM130694	14-Jan-83	male	21	21-30 YEARS	20	YES
297	SM070391	08-Mar-68	male	30	21-30 YEARS	55	NO

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298	SM030392	19-Sep-69	female	24	21-30 YEARS	42	NO
299	GM060393	25-Jul-77	male	19	21-30 YEARS	40	NO
300	AM060394	09-Jun-73	female	24	21-30 YEARS	50	NO
301	SM080395	03-Aug-73	male	26	21-30 YEARS	50	NO
302	RM060396	28-Aug-75	female	21	21-30 YEARS	20	NO
303	JM070397	03-Mar-70	male	28	21-30 YEARS	150	NO
304	DM100399	23-Jul-60	male	40	31-40 YEARS	16	NO
305	EM030400	03-Nov-68	female	25	21-30 YEARS		
306	CM100402	27-Sep-60	female	40	31-40 YEARS	150	NO
307	DM040403	13-Apr-69	female	26	21-30 YEARS	21	NO
308	DM060404	05-May-77	male	20	11-20 YEARS	100	NO
309	DM090405	21-Nov-57	male	43	41-50 YEARS		NO
310	JM120673	16-Oct-58	male	45	41-50 YEARS		YES
311	LM060406	04-Jul-70	female	26	21-30 YEARS	100	NO
312	FM020407	12-Nov-61	female	31	31-40 YEARS	50	NO
313	JM080408	23-Jun-74	female	24	21-30 YEARS	50	NO
314	MM080409	06-Jan-59	female	40	31-40 YEARS	50	NO
315	HM020411	29-Sep-68	female	24	21-30 YEARS	100	NO
316	JM090412	08-Mar-61	male	39	31-40 YEARS	100	NO
317	JM100413	15-Feb-70	male	31	31-40 YEARS	80	NO
318	CM080414	30-Jun-62	female	36	31-40 YEARS	40	NO
319	TM050416	16-Dec-74	female	21	21-30 YEARS	40	NO
320	GM070417	18-Apr-46	female	52	51-60 YEARS		
321	PM050418	26-Sep-51	female	45	41-50 YEARS	50	NO
322	SM040419	11-Sep-46	female	48	41-50 YEARS		YES
323	DM020420	26-Feb-64	male	29	21-30 YEARS		YES
324	DM100421	19-Feb-34	male	66	61 AND OLDER	50	NO
325	LM060422	11-Mar-67	female	30	21-30 YEARS	100	NO
326	MM040423	30-Mar-45	female	50	41-50 YEARS		YES
327	AM090424	18-Dec-48	male	52	51-60 YEARS		
328	NM050427	05-Sep-72	male	24	21-30 YEARS	196	NO
329	HM090430	01-Nov-56	female	44	31-40 YEARS		UNKNOWN
330	JM010431	09-Sep-52	female	40	31-40 YEARS		UNKNOWN
331	TM050433	17-Mar-72	female	23	21-30 YEARS	40	NO
332	JM040435	13-Mar-57	male	37	31-40 YEARS	69	NO
333	JM110436	31-May-74	male	28	31-40 YEARS	40	NO
334	SM030437	27-May-63	female	31	31-40 YEARS	70	NO
335	AM100428	29-May-85	female	16	11-20 YEARS	50	NO
336	NM090439	06-Jan-79	female	21	21-30 YEARS	70	NO
337	VM030440	01-Oct-45	male	49	41-50 YEARS	50	NO
338	AM070441	17-Apr-34	male	64	61 AND OLDER	50	NO
339	JM020443	27-May-69	female	23	21-30 YEARS	30	NO
340	MM050444	14-Apr-38	female	58	51-60 YEARS	102	NO
341	FM070445	24-Aug-71	female	27	21-30 YEARS	15	NO
342	MM030446	11-Jun-63	female	30	21-30 YEARS	50	NO
343	EM110448	30-Sep-67	female	34	31-40 YEARS	32	NO
344	IM100449	05-Jul-57	female	43	41-50 YEARS		YES
345	DM100450	22-Jul-58	female	41	41-50 YEARS	32	NO

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346	DM130688	29-Jun-69	male	34	31-40 YEARS	100	NO
347	TM020451	25-Dec-68	female	24	21-30 YEARS	100	NO
348	HM050452	15-Oct-41	male	55	41-50 YEARS	100	NO
349	AM120679	17-Jan-67	female	36	31-40 YEARS		NO
350	GM120453	15-Nov-29	male	73	61 AND OLDER		YES
351	SM100454	19-Jan-73	male	28	21-30 YEARS	50	NO
352	AM040455	19-Sep-69	female	25	21-30 YEARS	100	NO
353	EM110456	26-Sep-65	male	37	31-40 YEARS	40	YES
354	MM030457	09-Sep-53	female	40	31-40 YEARS	100	NO
355	TM060461	28-Aug-61	male	35	31-40 YEARS	20	NO
356	PM090462	15-Oct-65	male	34	31-40 YEARS	100	NO
357	AM120465	22-Jun-47	male	55	51-60 YEARS	60	NO
358	GM020466	02-Jul-70	male	23	21-30 YEARS	30	YES
359	AM050467	24-Apr-74	female	22	21-30 YEARS	100	NO
360	MM130696	24-Jan-82	female	22	21-30 YEARS	20	NO
361	BM110468	31-May-58	male	43	41-50 YEARS	40	YES
362	FM060469	30-Jul-75	male	21	21-30 YEARS	50	NO
363	JM040470	24-Aug-53	male	41	41-50 YEARS	50	NO
364	JM080471	25-Feb-68	female	31	31-40 YEARS	95	NO
365	DM070473	21-Jan-60	male	38	31-40 YEARS		YES
366	JM060474	16-Nov-54	male	43	41-50 YEARS	30	NO
367	BM090475	07-Sep-54	female	46	41-50 YEARS	30	NO
368	SM120476	12-Aug-61	female	42	41-50 YEARS	16	YES
369	AM120477	09-Feb-43	male	60	51-60 YEARS	64	NO
370	HM080478	09-Jun-61	female	37	31-40 YEARS		YES
371	AM110479	22-Jan-52	female	50	41-50 YEARS		YES
372	BM030480	05-May-40	male	54	51-60 YEARS	40	YES
373	JM070481	20-Dec-72	male	25	21-30 YEARS	30	YES
374	JM030482	18-Jun-76	female	28	21-30 YEARS	90	YES
375	TM060483	20-May-68	female	28	21-30 YEARS	55	NO
376	KM100485	17-Jul-87	male	13	11-20 YEARS	36	NO
377	EM080487	16-Jul-76	female	23	21-30 YEARS		YES
378	CM050488	09-Apr-79	female	16	11-20 YEARS	35	NO
379	GM030489	20-Oct-62	male	31	31-40 YEARS	100	NO
380	AN100490	14-May-72	male	28	21-30 YEARS		YES
381	DN060491	06-Dec-56	male	40	31-40 YEARS	50	NO
382	EN030493	14-Sep-51	female	42	41-50 YEARS		YES
383	JN040494	09-Mar-65	male	30	21-30 YEARS	100	NO
384	WN130697	22-Jul-72	male	32	31-40 YEARS		YES
385	RN090495	04-Dec-67	male	23	21-30 YEARS	100	NO
386	SN110496	27-Jan-71	female	31	31-40 YEARS	60	NO
387	LO090498	12-Nov-70	female	30	21-30 YEARS	80	NO
388	DP110503	21-Jan-75	male	27	21-30 YEARS	90	NO
389	JP070504	05-Jun-66	male	31	31-40 YEARS	50	NO
390	RP110505	21-Jun-81	male	20	11-20 YEARS	30	NO
391	EP090507	28-May-56	female	44	31-40 YEARS	70	
392	CP040509	24-Feb-53	male	42	41-50 YEARS	100	NO

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393	MP120510	27-Jun-61	male	42	41-50 YEARS	64	NO
394	SP020511	09-Aug-75	female	18	11-20 YEARS	55	NO
395	HP050512	10-Apr-66	female	29	21-30 YEARS	120	NO
396	JP100513	11-Feb-54	female	47	41-50 YEARS		NO
397	CP100514	27-Dec-54	female	46	41-50 YEARS	6	NO
398	JP120516	21-Mar-66	male	37	31-40 YEARS	70	YES
399	MP070517	06-Jun-69	female	28	21-30 YEARS	55	YES
400	YP070518	09-Oct-71	female	27	21-30 YEARS	50	YES
401	DP040519	07-Nov-26	male	68	61 AND OLDER	36	NO
402	PP040520	13-Sep-57	male	37	31-40 YEARS		UNKNOWN
403	JP120521	26-Oct-55	female	47	41-50 YEARS	70	NO
404	LP120670	18-Oct-66	female	37	31-40 YEARS		YES
405	LP060522	16-Oct-51	female	45	41-50 YEARS		
406	WP020523	04-Jul-69	female	23	21-30 YEARS	55	NO
407	AQ030524	24-Dec-75	female	18	11-20 YEARS	50	NO
408	MQ110525	29-Jun-65	female	37	31-40 YEARS	20	NO
409	PQ050526	09-Apr-42	male	54	51-60 YEARS	100	YES
410	HR050527	08-Nov-78	female	18	11-20 YEARS	14	NO
411	MR100528	05-Apr-51	female	49	41-50 YEARS	96	NO
412	GR040529	16-Jun-73	male	21	21-30 YEARS	60	NO
413	LR050531	06-Mar-62	female	34	31-40 YEARS	60	NO
414	AR080532	25-Oct-67	male	31	31-40 YEARS		YES
415	MR040533	24-Aug-47	female	47	41-50 YEARS		YES
416	NR090534	14-Jan-79	female	21	21-30 YEARS	70	NO
417	MR050535	01-Sep-69	male	26	21-30 YEARS	56	NO
418	MR030537	18-Jul-64	male	29	21-30 YEARS	30	YES
419	SR050536	30-May-69	male	27	21-30 YEARS	48	YES
420	WR120538	08-Aug-51	male	51	41-50 YEARS	50	NO
421	AR090539	20-Sep-73	male	26	21-30 YEARS	112	NO
422	PR110542	27-Oct-73	male	28	21-30 YEARS	100	YES
423	JR040543	20-Nov-78	male	16	11-20 YEARS	70	NO
424	CR120545	01-Mar-59	female	44	41-50 YEARS		YES
425	CR040546	17-Oct-63	male	31	31-40 YEARS	40	NO
526	DR120547	16-Sep-60	male	42	41-50 YEARS	130	YES
427	DR090548	24-Nov-78	female	21	21-30 YEARS	40	NO
428	JR040550	25-Mar-63	female	31	31-40 YEARS	30	NO
429	JR070552	25-Jun-58	female	40	31-40 YEARS	60	NO
430	PR120554	04-Sep-52	female	50	41-50 YEARS		YES
431	WR070555	18-Jan-69	male	29	21-30 YEARS	20	NO
432	CR070556	24-Nov-58	female	39	31-40 YEARS	48	NO
433	JR030557	07-Nov-68	male	25	21-30 YEARS	100	NO
434	JR120686	07-Jun-56	female	47	41-50 YEARS		NO
435	NR050558	15-Nov-79	male	16	11-20 YEARS	22	YES
436	MR120684	20-May-61	female	42	41-50 YEARS	60	NO
437	GR040559	11-Jan-66	male	29	21-30 YEARS	150	YES
438	WR080560	27-Sep-53	male	45	41-50 YEARS	16	NO
439	IR100562	15-Dec-55	female	45	41-50 YEARS	30	NO

Number	Code	DOB	Sex	Age	Age band	No Tablet	Stag OD
440	JR090563	17-Dec-65	male	34	31-40 YEARS	98	NO
441	ER090564	16-May-71	male	29	21-30 YEARS	100	NO
442	MR040565	30-Jan-64	male	31	31-40 YEARS	60	YES
443	KS080569	23-Nov-65	female	33	31-40 YEARS	24	YES
444	WS030570	29-Oct-55	male	38	31-40 YEARS	90	NO
445	SW030571	26-Jan-50	male	43	41-50 YEARS	80	NO
446	KS130695	19-May-69	female	34	31-40 YEARS	10	NO
447	JS090574	23-Feb-51	female	49	41-50 YEARS		YES
448	BS020575	04-Mar-72	male	21	21-30 YEARS	140	NO
449	SS060576	17-Apr-45	female	46	41-50 YEARS	150	YES
450	KS110578	31-Oct-57	male	44	41-50 YEARS		YES
451	NS110579	20-Jul-60	female	42	41-50 YEARS		YES
452	PS080580	31-May-58	female	40	31-40 YEARS	9	YES
453	WS020582	11-Apr-68	male	25	21-30 YEARS	50	NO
454	AS090583	16-Jan-64	male	35	31-40 YEARS	50	NO
455	IS100584	13-Mar-75	male	26	21-30 YEARS	100	NO
456	JS030585	20-Dec-52	male	41	41-50 YEARS	100	NO
457	MS050587	12-Apr-59	male	36	31-40 YEARS	80	NO
458	LS130710	10-Sep-64	male	39	31-40 YEARS	60	NO
459	SS060589	05-May-71	female	25	21-30 YEARS	46	NO
460	TS080590	20-Feb-42	female	57	51-60 YEARS		YES
461	JS020591	27-May-58	female	35	31-40 YEARS	60	NO
462	DS040592	07-Sep-70	male	24	21-30 YEARS	200	NO
463	ES100594	25-May-67	male	34	31-40 YEARS		NO
464	PS030595	07-Nov-49	female	45	41-50 YEARS		UNKNOWN
465	GS110597	08-Feb-02	male	22	21-30 YEARS	32	NO
466	JS040598	09-Mar-64	male	31	31-40 YEARS	80	NO
467	MS110600	02-May-48	male	53	41-50 YEARS	100	NO
468	PS030601	16-Jun-67	male	26	21-30 YEARS	60	NO
469	AS080602	30-Mar-68	female	31	31-40 YEARS	90	YES
470	JS030603	25-Feb-41	female	53	51-60 YEARS	60	NO
471	WS090605	04-May-58	male	41	41-50 YEARS	70	NO
472	AS060606	01-Nov-59	female	37	31-40 YEARS	45	YES
473	RT060608	17-Jan-54	male	43	41-50 YEARS	72	NO
474	BT060610	06-Mar-65	female	32	31-40 YEARS	48	NO
475	CT120677	30-Apr-60	female	43	41-50 YEARS		YES
476	DT010612	25-Feb-70	male	23	21-30 YEARS	200	NO
477	ET050613	27-May-70	male	26	21-30 YEARS	50	NO
478	RT040614	19-Jun-66	male	28	21-30 YEARS	30	NO
479	AT060615	07-Jan-76	female	20	11-20 YEARS	25	NO
480	CT030616	09-Dec-51	male	42	41-50 YEARS		
481	DT090617	22-Feb-57	male	43	41-50 YEARS	120	YES
482	ET040618	20-Apr-74	female	21	21-30 YEARS	24	NO
483	JT060620	17-Dec-24	male	54	51-60 YEARS	100	NO
484	VT110621	28-Nov-65	female	36	31-40 YEARS	96	NO
485	DT040622	06-Jan-64	male	30	21-30 YEARS	55	NO

Number	Code	DOB	Sex	Age	Age band	No Tablet	Stag OD
486	CT080623	24-Jan-65	female	34	31-40 YEARS		NO
487	JT050624	11-Dec-51	male	45	41-50 YEARS	30	NO
488	KT100625	24-Apr-46	female	55	41-50 YEARS		YES
489	GT110626	06-Jun-80	male	21	21-30 YEARS	30	NO
490	GT010627	09-May-58	male	34	31-40 YEARS	100	NO
491	ST070628	10-Dec-62	male	35	31-40 YEARS	48	NO
492	ST110629	26-Sep-86	female	15	11-20 YEARS	100	NO
493	DW050632	26-Nov-70	male	25	21-30 YEARS	150	NO
494	EW050633	02-Dec-46	female	49	41-50 YEARS	60	NO
495	JW030634	20-Jun-47	male	46	41-50 YEARS	110	NO
496	PW070635	18-Apr-53	male	44	41-50 YEARS	30	NO
497	PW100636	25-Jan-44	male	45	41-50 YEARS	60	YES
498	MW060637	26-Jun-55	female	42	41-50 YEARS	120	YES
499	SW040638	23-Jul-54	female	40	31-40 YEARS	19	YES
500	DW120639	07-Sep-70	female	22	21-30 YEARS	32	NO
501	IW060640	10-Jul-80	female	16	11-20 YEARS	70	NO
502	PW070642	18-Apr-53	male	44	41-50 YEARS	30	NO
503	PW090643	27-Dec-71	male	28	21-30 YEARS	60	YES
504	WW080644	28-Oct-48	male	50	41-50 YEARS	18	YES
505	CW100645	17-Jul-62	female	38	31-40 YEARS		UNKNOWN
506	DW120647	21-Nov-77	male	31	31-40 YEARS	12	YES
507	EW120648	05-Mar-57	female	46	41-50 YEARS		YES
508	MW040649	19-Jun-61	female	34	31-40 YEARS		UNKNOWN
509	JW070650	18-Feb-45	male	53	51-60 YEARS	82	NO
510	MW010651	17-Oct-66	female	26	21-30 YEARS	42	NO
511	BW080652	23-Mar-65	male	34	31-40 YEARS	100	YES
512	LW050653	02-Aug-73	male	23	21-30 YEARS	75	NO
513	SW130703	30-Mar-60	female	44	31-40 YEARS	140	YES
514	JW070655	25-Dec-46	male	52	41-50 YEARS	40	NO
515	JW040656	14-May-68	male	26	21-30 YEARS	40	NO
516	KW060657	12-Oct-68	female	28	21-30 YEARS	150	NO
517	RW090658	16-Oct-65	male	34	31-40 YEARS	60	NO
518	EW090659	16-Aug-78	female	21	21-30 YEARS	64	NO
519	KW060660	17-Apr-71	male	26	21-30 YEARS		YES
520	HW110662	19-Aug-42	female	60	51-60 YEARS	20	NO
521	TW100666	08-Nov-77	female	23	21-30 YEARS	40	NO
522	MZ030667	15-Jan-64	female	30	21-30 YEARS	80	NO

Number	Ass AIC	ALC intake Unit (weekly)	Ref BP mmHg	Ref BP gr	RIE BP mmHg	RIE BP gr
1	NO		106/52	normotensive	137/55	normotensive
2	NO	10	150/64	normotensive	137/75	normotensive
3		7	130/70	normotensive	115/60	normotensive
4	YES	56	190/80	normotensive	123/69	hypotensive
5	YES	30	140/60	normotensive	104/49	normotensive
6	YES	10	125/65	normotensive	125/59	normotensive
7	YES	100	124/65	normotensive	98/50	hypotensive
8			50/35	hypotensive	120/60	normotensive
9	YES	10	115/54	normotensive	130/58	normotensive
10	YES	34	84/49	hypotensive	100/60	hypotensive
11	YES	180			90/40	hypotensive
12	YES	140	130/70	normotensive	116/46	normotensive
13	NO	12	150/80	normotensive	160/80	normotensive
14	NO		180/95	normotensive	135/75	normotensive
15	NO		130/69	normotensive	140/85	normotensive
16	YES	60	170/83	normotensive	90/40	hypotensive
17	YES	12	95/40	hypotensive	90/60	hypotensive
18	YES	20	135/60	normotensive	143/93	normotensive
19	NO	14	140/70	normotensive	140/60	normotensive
20					80/50	hypotensive
21	YES		91/41	hypotensive		
22	NO	20			140/70	normotensive
23	NO	10	95/49	hypotensive	122/72	normotensive
24	YES	350	147/88	normotensive	108/40	normotensive
25	YES	28	170/92	normotensive	159/73	normotensive
26	NO	10	157/110	normotensive	110/70	normotensive
27	YES	50	106/78	normotensive	142/70	normotensive
28	NO	10	118/76	normotensive	110/70	normotensive
29	YES	350	139/96	normotensive	91/52	hypotensive
30	NO	12	121/82	normotensive	128/73	normotensive
31	YES	30	140/60	normotensive	130/50	normotensive
32		5	109/59	normotensive	117/63	normotensive
33	YES	84	156/77	hypotensive	137/75	normotensive
34	YES	210	140/70	normotensive	80/40	hypotensive
35	YES	280	122/76	normotensive	104/44	normotensive
36	NO	5	99/50	hypotensive	128/79	normotensive
37	NO	6	153/64	normotensive	131/74	normotensive
38	NO	30	120/70	normotensive	123/76	normotensive
39	YES	540	90/52	hypotensive	95/0	hypotensive
40	NO	28	162/83	normotensive	160/60	normotensive
41	YES	21	80/40	hypotensive	80/0	hypotensive
42		32	105/50	hypotensive	86/50	hypotensive
43	YES	10	105/59	normotensive	102/47	normotensive
44	NO				120/64	normotensive
45	YES	5	138/62	normotensive	118/62	normotensive
46	NO		120/65	normotensive	117/76	normotensive
47	NO	10	120/70	normotensive	120/70	normotensive
48	YES	140	110/40	normotensive	106/60	normotensive
49	YES		110/70	normotensive	126/58	normotensive
50	YES	20	115/70	normotensive	180/60	normotensive
51	NO		120/80	normotensive	100/59	hypotensive
52	NO	20	151/81	normotensive	94/43	hypotensive

Number	Ass AIC	ALC intake (weekly)	Unit	Ref BP mmHg	Ref BP gr	RIE BP mmHg	RIE BP gr
53	NO	36				135/70	normotensive
54	YES			120/70	normotensive	125/70	normotensive
55	NO			120/75	normotensive	115/69	normotensive
56	NO			125/71	normotensive	136/67	normotensive
57	NO	4				130/50	normotensive
58	YES	28		152/81	normotensive	155/85	normotensive
59				114/56	normotensive	100/60	normotensive
60	NO	180		125/80	normotensive		
61	NO	180		130/85	normotensive	100/60	hypotensive
62	NO			120/60	normotensive	108/50	normotensive
63	NO			179/102	normotensive	155/85	normotensive
64	YES	20		147/92	normotensive	158/99	normotensive
65	NO	4		140/74	normotensive	130/70	normotensive
66	NO	20		181/105	normotensive	170/80	normotensive
67	NO			125/68	normotensive	123/64	normotensive
68	YES						
69	YES	21		120/70	normotensive	125/80	normotensive
70	YES	20		140/80	normotensive	110/610	normotensive
71	YES	90		150/80	normotensive	116/58	normotensive
72	NO	5		130/80	normotensive	120/70	normotensive
73	NO	168		103/50	hypotensive	131/64	normotensive
74	NO			140/70	normotensive	117/60	normotensive
75	NO			103/55	hypotensive	130/55	normotensive
76	NO					120/60	normotensive
77		21		118/91	normotensive	120/50	normotensive
78	YES	25		95/70	hypotensive	157/109	normotensive
79	NO	40		140/76	normotensive	120/80	normotensive
80	NO	10		81/44	hypotensive	110/70	normotensive
81	YES			107/70	normotensive	117/42	normotensive
82	YES	140				140/80	normotensive
83	NO			140/85	normotensive	140/66	normotensive
84	NO			136/94	hypertensive	113/61	normotensive
85	NO	5		102/62	normotensive	123/62	normotensive
86	YES	80		137/62	normotensive	136/52	normotensive
87	NO	350		122/80	normotensive	122/80	normotensive
88	NO			100/85	normotensive	128/82	normotensive
89	NO			130/80	normotensive	115/60	normotensive
90	YES					76/40	hypotensive
91	YES	200		141/76	normotensive	80/55	hypotensive
92	YES	140		135/62	normotensive	130/72	normotensive
93	YES	102		90/60	hypotensive		
94	YES	90		128/79	normotensive	118/64	normotensive
95	YES	40				130/84	normotensive
96	NO			67/49	hypotensive	77/55	hypotensive
97	YES	200		99/71	hypotensive	86/45	hypotensive
98	YES	126		150/92	normotensive	180/80	normotensive
99	NO	60		125/65	normotensive	130/78	normotensive
100	YES	100		121/64	normotensive	132/60	normotensive
101				80/67	hypotensive	75/20	hypotensive
102	YES	56		190/98	hypertensive	144/70	normotensive
103	NO			140/86	normotensive	122/65	normotensive

Number	Ass ALC	ALC intake (weekly)	Unit	Ref BP mmHg	Ref BP gr	RIE BP mmHg	RIE BP gr
104				104/60	normotensive	94/60	hypotensive
105	YES	16		130/70	normotensive	144/96	normotensive
106	YES	200		90/42	hypotensive	108/45	hypotensive
107	YES	50				140/30	hypotensive
108	YES	280				113/65	normotensive
109	YES	20		118/64	normotensive		
110	YES	50		112/67	normotensive	106/52	normotensive
111	NO			92/60	hypotensive	110/80	normotensive
112		210		140/75	normotensive	85/50	hypotensive
113	YES	240		141/88	hypotensive	139/76	normotensive
114		80		95/60	hypotensive		
115	NO	64		107/58	normotensive	149/84	normotensive
116	YES	35				110/70	normotensive
117	NO	8		120/72	normotensive	118/50	normotensive
118	NO	10		110/60	normotensive	120/60	normotensive
119	NO	140		114/76	normotensive	158/88	normotensive
120	YES			155/75	normotensive	120/75	normotensive
121	NO			105/60	normotensive	124/74	normotensive
122	YES	315		94/42	hypotensive	101/44	normotensive
123	YES			95/50	hypotensive	112/60	normotensive
124	NO			60/20	hypotensive	87/21	hypotensive
125	YES	45				136/60	normotensive
126	NO			113/47	normotensive	120/40	normotensive
127	NO			69/45	hypotensive	90/40	hypotensive
128	NO	12		134/87	normotensive	134/88	normotensive
129	NO			71/61	hypotensive	101/43	normotensive
130	NO			120/70	normotensive	121/57	normotensive
131	NO	8		145/49	normotensive	127/31	hypotensive
132	YES	28		146/82	normotensive	140/80	normotensive
133	YES			152/97	normotensive	154/74	normotensive
134	YES	14		128/76	normotensive	120/50	normotensive
135	YES			169/111	hypertensive	88/58	hypotensive
136		60		138/78	normotensive	115/50	normotensive
137	NO			178/60	normotensive	162/56	normotensive
138				94/42	hypotensive	124/65	normotensive
139	NO	60		148/92	hypertensive	120/80	normotensive
140	NO	14		143/84	normotensive	144/90	HYPERTENSIVE
141	NO					109/43	normotensive
142	NO			132/64	normotensive	110/55	normotensive
143	NO	60		99/46	hypotensive	99/51	hypotensive
144	YES			130/80	normotensive	141/78	normotensive
145	NO						
146		140		124/68	normotensive	120/60	normotensive
147	NO	25		110/80	normotensive		
148	NO			160/120	hypertensive	110/65	normotensive
149	NO	210				140/65	normotensive
150	NO	84				114/70	normotensive
151	YES	90		130/70	normotensive	100/80	hypotensive
152	NO			129/79	normotensive	120/80	normotensive
153	YES	70		109/61	normotensive	110/70	normotensive
154	YES	280		78/38	hypotensive	98/68	normotensive
155	NO			132/63	normotensive	97/43	hypotensive

Number	Ass AIC	ALC intake (weekly)	Unit	Ref BP mmHg	Ref BP gr	RIE BP mmHg	RIE BP gr
156		14		120/60	normotensive	120/60	normotensive
157	YES			113/58	normotensive		
158	YES	30		130/70	normotensive	143/75	normotensive
159				90/40	hypotensive	140/83	normotensive
160	NO			100/64	normotensive	113/67	normotensive
161	YES	100		133/72	normotensive	126/68	normotensive
162	YES	70		140/80	normotensive	170/83	normotensive
163	NO			125/72	normotensive	150/62	normotensive
164	YES	100		74/35	hypotensive	93/45	hypotensive
165	YES			130/74	normotensive	145/55	normotensive
166	NO	14		160/72	normotensive	120/82	normotensive
167				149/82	normotensive	138/72	normotensive
168	YES	14		118/65	normotensive	125/38	normotensive
169	NO			110/80	normotensive		
170	NO	40		120/80	normotensive	136/90	normotensive
171	YES	8		149/69	normotensive	132/80	normotensive
172	NO	40				130/70	normotensive
173	NO	140		127/88	normotensive	152/89	normotensive
174	NO			140/90	normotensive	140/70	normotensive
175	YES	20		130/70	normotensive	105/50	normotensive
176	YES	6		109/54	normotensive	95/60	
177	YES			132/80	normotensive	116/63	normotensive
178	YES	10		164/86	normotensive	136/63	normotensive
179	YES	50		135/82	normotensive	110/70	normotensive
180	NO			122/60	normotensive	133/61	normotensive
181		560		88/60	hypotensive	110/55	normotensive
182	NO	10		130/80	normotensive	105/44	normotensive
183		8		138/80	normotensive	127/65	normotensive
184				88/72	hypotensive	140/70	normotensive
185		24		111/59	normotensive	132/65	normotensive
186	NO			113/47	normotensive	115/65	normotensive
187	NO			100/60	normotensive	120/50	normotensive
188	YES			112/89	normotensive	114/36	hypotensive
189	NO	20		135/82	normotensive	140/80	normotensive
190	YES	50		110/60	normotensive	120/60	normotensive
191	NO			121/49	normotensive	100/50	normotensive
192	YES	100		92/51	hypotensive	138/70	normotensive
193	NO			150/90	normotensive	120/70	normotensive
194		10		97/50	hypotensive	90/30	hypotensive
195		21		112/63	normotensive	117/72	normotensive
196	YES	50					
197	YES	10		114/70	normotensive	120/60	normotensive
198	NO	8				126/80	normotensive
199	YES	14				85/50	hypotensive
200	NO	80		170/80	normotensive	131/63	normotensive
201	YES	300		158/122	hypertensive	90/70	hypotensive
202	NO	14		105/64	normotensive	120/70	normotensive
203	NO			130/70	normotensive	114/36	normotensive
204	NO	14				142/56	normotensive
205	YES					128/62	normotensive
206	NO			117/65	normotensive	140/80	normotensive
207	YES			110/60	normotensive	89	normotensive

Number	Ass AIC	ALC intake Unit (weekly)	Ref BP mmHg	Ref BP gr	RIE BP mmHg	RIE BP gr
208	YES		113/63	normotensive		
209	YES	60	128/70	normotensive	110/60	normotensive
210	NO		115/65	hypotensive	133/64	normotensive
211	NO		110/60	normotensive	105/43	normotensive
212	YES		140/80	normotensive	160/75	normotensive
213	YES				107/51	normotensive
214	YES	40	97/43	hypotensive	114/96	normotensive
215	NO	10	120/60	normotensive	110/80	normotensive
216	YES	28			170/100	HYPERTENSIVE
217	YES	30	128/64	normotensive	124/62	normotensive
218	NO		100/80	normotensive	115/50	normotensive
219	YES	50	144/91	hypertensive	125/60	normotensive
220	YES	20	119/86	normotensive	97/47	hypotensive
221	NO	14	116/73	normotensive	130/65	normotensive
222	YES	100	138/90	normotensive	130/40	normotensive
223	NO		116/58	normotensive	140/68	normotensive
224	NO	100	123/78	normotensive	186/103	HYPERTENSIVE
225	YES	100	110/60	normotensive	110/70	normotensive
226			86/50	hypotensive		
227	YES	7	115/96	normotensive	106/43	normotensive
228	NO		105/45	normotensive	90/45	hypotensive
229	NO	27	140/80	normotensive	119/52	normotensive
230					121/57	normotensive
231			0/0	hypotensive	0	normotensive
232	YES	60	94/34	hypotensive	121/45	normotensive
233	NO	40	124/74	normotensive	125/85	normotensive
234	NO	125			150/70	normotensive
235	YES	140	120/80	normotensive	140/61	normotensive
236	YES	5	110/60	normotensive	114/60	normotensive
237	NO		135/68	normotensive	119/42	hypotensive
238	YES	16	140/90	normotensive	155/78	normotensive
239	YES	28	120/70	normotensive	138/74	normotensive
240	NO	20	120/70	normotensive	169/90	normotensive
241	NO	98	130/50	normotensive	118/50	normotensive
242	YES				180/120	hypertensive
243	NO	8	108/74	normotensive	110/60	normotensive
244	YES	20	142/66	normotensive	127/72	normotensive
245	YES	54	148/94	normotensive	124/67	normotensive
246						
247	NO		140/60	normotensive	132	normotensive
248	NO		102/62	normotensive	100/60	normotensive
249		14	130/70	normotensive	139/72	normotensive
250	NO	10	122/37	normotensive	108/46	normotensive
251	NO		149/67	normotensive	115/55	normotensive
252	NO	20	140/90	normotensive	122/42	normotensive
253			75/40	hypotensive	84/38	hypotensive
254	YES	14	138/87	normotensive	141/90	normotensive
255	NO		90/70	hypotensive	90/50	hypotensive
256	NO	18			130/75	normotensive
257	YES	10	115/70	normotensive	130/70	normotensive
258			105/60	normotensive	120/60	normotensive

Number	Ass AIC	ALC intake Unit (weekly)	Ref BP mmHg	Ref BP gr	RIE BP mmHg	RIE BP gr
259			90/56	hypotensive	130/80	normotensive
260	YES	20	130/62	normotensive	119/55	normotensive
261	YES	21	123/72	normotensive	127/82	normotensive
262			125/55	normotensive	134/74	normotensive
263	NO	7	130/50	normotensive	120/60	normotensive
264	NO				105/52	normotensive
265		10	150/70	normotensive	144/84	normotensive
266		50	130/80	normotensive	150/80	normotensive
267	YES	50	122/68	normotensive	117/47	hypotensive
268		210	151/120	normotensive	103/67	hypotensive
269	NO		100/60	normotensive	107/50	normotensive
270	NO	10	110/60	normotensive	118/75	normotensive
271	NO	28	122/67	normotensive		
272			121/63	normotensive	105/64	hypotensive
273	NO	20	152/84	normotensive	140/72	normotensive
274	YES	70	84/50	hypotensive	80/0	hypotensive
275	YES	10			115/60	normotensive
276	YES	100	60/30	hypotensive	78/42	hypotensive
277	NO	20			90/0	hypotensive
278	NO		98/41	hypotensive		hypotensive
279	NO		120/80	normotensive	75/45	hypotensive
280	NO	28	120/92	normotensive	99/33	hypotensive
281	NO				135/63	normotensive
282	NO	10			104/60	normotensive
283			145/70	normotensive	182/95	normotensive
284	YES	4	130/70	normotensive	114/50	normotensive
285		200	90/60	hypotensive	110/50	normotensive
286	YES		140/60	normotensive	120/70	normotensive
287	YES	150	138/76	normotensive	115/62	normotensive
288	YES	70	125/75	normotensive	122/88	normotensive
289			98/50	hypotensive	115/64	normotensive
290	NO	18	100/40	normotensive	120/60	normotensive
291	NO	30	122/74	normotensive	167/90	hypertensive
292	YES	120	102/70	normotensive	139/79	normotensive
293	YES	56	107/54	normotensive	120/55	normotensive
294	YES	40	115/80	hypotensive	100/48	hypotensive
295	YES	60	150/70	normotensive	120/50	normotensive
296		36	80/50	hypotensive	108/62	normotensive
297	YES	56	146/95	normotensive	146/95	normotensive
298	NO	10	100/40	normotensive	79/38	normotensive
299		20	150/60	normotensive	115/45	normotensive
300	NO	14	120/70	normotensive	100/70	normotensive
301						
302	NO	14	121/71	normotensive	126/71	normotensive
303	YES		148/78	normotensive	120/70	normotensive
304	YES	420	82	hypertensive	121/89	normotensive
305						
306		6	93/53	hypotensive		
307	YES	14	80/40	hypotensive	115/60	normotensive
308	YES	21	127/74	normotensive	135/65	normotensive
309	YES	25	136/96	normotensive	130/70	normotensive
310	NO	40	130/80	normotensive	135/70	normotensive

Number	Ass AIC	ALC intake Unit (weekly)	Ref BP mmHg	Ref BP gr	RIE BP mmHg	RIE BP gr
311	NO	28	99/53	normotensive	105/50	normotensive
312	NO	7			133/84	normotensive
313	NO		125/76	normotensive	132/62	normotensive
314	NO				114/59	normotensive
315	NO	10	128/78	normotensive	120/70	normotensive
316	YES	450	109/60	normotensive	148/91	normotensive
317	NO	20	88/40	hypotensive	160/70	normotensive
318	NO		110/59	normotensive	130/70	normotensive
319	NO	10	138/74	normotensive	134/50	normotensive
320		28	92/56	hypotensive	143/81	normotensive
321	NO		80/50	hypotensive	94/26	hypotensive
322	YES	35			88/0	hypotensive
323	YES	140	140/80	normotensive	150/85	normotensive
324	NO	210	170/90	hypertensive	151/61	normotensive
325			125/80	normotensive	9./35	hypotensive
326	YES	180			158/78	normotensive
327						
328	NO		150/100	normotensive	150/85	normotensive
329	YES					
330						hypotensive
331	YES	14	122/60	normotensive	127/54	normotensive
332			154/83	normotensive		
333	YES	30	132/68	normotensive	140/70	normotensive
334	NO	8			105/70	normotensive
335	NO		133/61	normotensive	102/63	normotensive
336	YES	4	130/76	normotensive	110/60	normotensive
337	YES	210			134/70	normotensive
338	NO				138/78	normotensive
339	NO	10			116/58	normotensive
340			145/50	normotensive	85/45	hypotensive
341	YES	4	124/60	normotensive	118/55	normotensive
342	NO				141/80	normotensive
343	YES	200	118/66	normotensive	147/96	HYPERTENSIVE
344	YES	50	112/60	normotensive	80/20	normotensive
345	NO		97/79	hypotensive	121/64	normotensive
346	YES	112	144/96	hypertensive	105/45	hypotensive
347	NO	10				
348	YES	60	140/90	normotensive	114/48	normotensive
349	YES		100/60	hypotensive	100/60	hypotensive
350	YES	40	132/86	normotensive	118/45	hypotensive
351	YES	21	143/85	normotensive	131/61	normotensive
352	NO	10			130/90	normotensive
353	YES	75	119/55	normotensive	118/54	normotensive
354	YES	70			73/38	hypotensive
355	YES	80	154/112	normotensive	139/95	normotensive
356	NO	10	113/74	normotensive	120/65	normotensive
357	YES	210	107/65	normotensive	130/70	normotensive
358	NO	10	120/80	normotensive	160/85	normotensive
359			120/60	normotensive	95/36	hypotensive
360	YES		118/61	normotensive	117/70	normotensive
361	YES	140			110/55	normotensive
362	NO	30	130/56	normotensive	137/65	normotensive

Number	Ass AIC	ALC intake Unit (weekly)	Ref BP mmHg	Ref BP gr	RIE BP mmHg	RIE BP gr
363	NO	6	180/100	normotensive	100/0	hypotensive
364	NO	6	137/68	normotensive	116/70	normotensive
365	YES	40	116/60	normotensive	112/60	normotensive
366	YES	40	140/86	normotensive	130/70	normotensive
367	NO	63	184/92	hypertensive	128/60	normotensive
368	NO	26	105/70	hypotensive	105/70	normotensive
369	YES	98	105/65	normotensive	124/70	normotensive
370	YES	14	95/54	hypotensive	120/70	normotensive
371	NO	14	111/55	normotensive	139/90	normotensive
372	NO	720	100/60	normotensive	140/70	normotensive
373	YES	180	127/75	normotensive	151/84	normotensive
374	NO				126/64	normotensive
375	NO		118/48	normotensive	112/50	normotensive
376	NO		118/87	normotensive	118/70	normotensive
377	YES	10	68/40	hypotensive	110/30	hypotensive
378	NO		147/95	normotensive	138/79	normotensive
379	YES	40			130/70	normotensive
380	NO		170/100	hypertensive	95/44	hypotensive
381	NO	40	170/94	normotensive	135/80	normotensive
382	NO	720			120/70	normotensive
383	NO	20			135/80	normotensive
384	YES	280	176/108	hypertensive	100/30	hypotensive
385	NO		122/68	normotensive	82/50	hypotensive
386	NO	14	123/52	normotensive	120/70	normotensive
387	NO		116/66	normotensive	115/70	normotensive
388			144/69	normotensive	70/40	hypotensive
389	YES	120	130/70	normotensive	112/39	normotensive
390	YES		110/50	normotensive	138/74	normotensive
391	NO				101/40	hypotensive
392	NO		132/70	normotensive	105/80	normotensive
393	NO	14	150/70	normotensive	120/60	normotensive
394	NO	10			120/70	normotensive
395	NO		146/67	normotensive	110/54	normotensive
396	NO		116/79	normotensive	101/52	normotensive
397	NO	14	126/90	normotensive	82/40	hypotensive
398	NO	6			130/72	normotensive
399		14	131/67	normotensive	119/62	normotensive
400	NO		140/80	normotensive	96/60	hypotensive
401	YES	126	90/60	hypotensive	129/65	normotensive
402			150/70	normotensive	130/70	normotensive
403	NO		130/79	normotensive	138/68	HYPERTENSIVE
404		63		hypotensive	120/60	normotensive
405		14	60/40	hypotensive	99/47	hypotensive
406	NO				110/70	normotensive
407	NO	10	108/70	normotensive	120/60	normotensive
408	YES	78	127/60	normotensive	117/82	normotensive
409	NO	30	150/100	normotensive	105/55	normotensive
410	YES	10	110/50	normotensive	114/52	normotensive
411	YES	20				
412	NO	20			100/55	normotensive
413	NO				123/73	normotensive
414	NO	10	102/68	normotensive	115/68	normotensive

Number	Ass AIC	ALC intake (weekly)	Unit	Ref BP mmHg	Ref BP gr	RIE BP mmHg	RIE BP gr
415	YES					78/40	hypotensive
416	YES	14		141/81	normotensive	110/45	normotensive
417	YES	80		113/43	normotensive	116/66	normotensive
418	NO	50		150/75	normotensive	110/70	normotensive
419	NO	50		123/72	normotensive	150/70	normotensive
420	YES	300		177/115	hypertensive	128/72	normotensive
421	NO			140/50	normotensive	120/60	normotensive
422	YES	26		192/103	hypertensive	197/96	HYPERTENSIVE
423	NO			160/80	normotensive	145/57	normotensive
424	NO					178/86	HYPERTENSIVE
425	YES	40				148/68	normotensive
526	YES	200		134/79	normotensive	145/75	normotensive
427	NO	14		139/88	normotensive	130/90	normotensive
428	NO					126/63	normotensive
429	NO			129/83	normotensive	152/101	HYPERTENSIVE
430						80/40	hypotensive
431	NO	20		91/52	hypotensive	127/85	normotensive
432	NO	30				125/72	normotensive
433						127/87	normotensive
434				126/86	normotensive	120/70	normotensive
435	NO			160/90	normotensive	120/60	normotensive
436	NO			136/76	normotensive	115/70	normotensive
437	NO	50		95/45	hypotensive	110/80	normotensive
438	YES	315		110/59	normotensive	80/40	hypotensive
439	YES			113/78	normotensive	120/60	normotensive
440	NO	8		144/78	normotensive	98/47	hypotensive
441	YES					110/70	normotensive
442		28		170/90	normotensive	170/90	normotensive
443	NO			108/50	hypotensive	110/60	normotensive
444	NO	360				170/80	normotensive
445	YES	4				142/89	normotensive
446	NO			53/41	hypotensive	86/44	hypotensive
447	NO			64/49	hypotensive	114/62	normotensive
448	NO	10				90/35	hypotensive
449	YES	14		90/68	normotensive	106/67	normotensive
450	YES	210		122/77	normotensive	127/77	normotensive
451	NO	400		114/65	normotensive	100/60	normotensive
452	NO			110/68	normotensive	115/42	normotensive
453	NO	10				122/68	normotensive
454	YES	118		133/87	normotensive	138/63	normotensive
455	NO	24		150/75	normotensive	110/70	normotensive
456						128/66	normotensive
457	NO	18		140/80	normotensive	138/63	normotensive
458	YES			125/94	hypertensive	125/94	HYPERTENSIVE
459	NO			113/69	normotensive	114/55	normotensive
460	NO	63		115/69	normotensive	140/75	normotensive
461	NO	10				105/50	normotensive
462	NO	70				100/20	hypotensive
463		14		141/88	normotensive	180/102	HYPERTENSIVE
464	YES	180				154/67	normotensive
465	NO	10		130/77	normotensive	140/70	normotensive
466	NO	154				133/52	normotensive

Number	Ass AIC	ALC intake (weekly)	Unit	Ref BP mmHg	Ref BP gr	RIE BP mmHg	RIE BP gr
467	YES					105/60	normotensive
468	NO	10				130/75	normotensive
469		20		108/50	hypotensive	114/67	normotensive
470	YES	50				132/83	normotensive
471	NO	10		113/72	normotensive	120/60	normotensive
472	YES	50		140/50	normotensive	134/60	normotensive
473	YES	40		146/81	normotensive	107/66	normotensive
474	NO			110/70	normotensive	126/78	normotensive
475	YES	200		100/60	normotensive	98/50	hypotensive
476	NO	10				150/70	normotensive
477	YES	14		139/88	normotensive	123/76	normotensive
478	NO					110/55	normotensive
479	NO	24		120/70	normotensive	133/47	normotensive
480		8				108/50	normotensive
481		160		160/80	normotensive	114/87	normotensive
482	NO			120/88	normotensive	125/55	normotensive
483				142/80	normotensive	101/35	normotensive
484	YES	20		103/72	normotensive	119/46	normotensive
485	NO	20		125/86	normotensive	103/60	normotensive
486	NO					116/61	normotensive
487	YES			135/79	normotensive	127/75	normotensive
488	NO	50		80/60	hypotensive	140/50	normotensive
489	YES	70		139/55	normotensive	146/56	normotensive
490	YES	140		130/70	normotensive	145/65	normotensive
491	YES	40		147/85	hypotensive	85/38	hypotensive
492	YES	9		123/92	normotensive	115/64	normotensive
493	NO			154/88	normotensive	151/76	normotensive
494	NO			110/60	normotensive	105/56	normotensive
495	NO	10				75/54	hypotensive
496	YES	260		240/170	hypertensive	120/60	normotensive
497	YES	420		74/40	hypotensive	117/72	normotensive
498	YES	45		118/62	normotensive	100/72	normotensive
499						115/80	normotensive
500	NO	21		62/32	hypotensive	90/40	hypotensive
501	YES	30		136/60	normotensive	125/55	normotensive
502		60		120/60	normotensive	90/48	hypotensive
503	NO					100/20	hypotensive
504	NO	70		150/90	normotensive	110/60	normotensive
505	NO	14		138/80	normotensive	136/68	normotensive
506	NO	25		144/74	normotensive	160/80	normotensive
507	YES	140		130/79	normotensive	130/79	normotensive
508		540				135/71	normotensive
509	YES	35		160/110	hypertensive	183/98	normotensive
510	NO	10				124/57	normotensive
511	YES	7		138/75	normotensive	140/71	normotensive
512	YES			120/60	normotensive	125/66	normotensive
513	YES	280		140/82	normotensive	110/76	normotensive
514	NO	24		170/100	hypertensive	147/73	normotensive
515		14		125/75	normotensive	130/57	normotensive
516	NO			105/38	normotensive	119/63	normotensive
517	YES	20			normotensive	120/70	normotensive
518	YES	60		107/82	normotensive	114/64	normotensive

Number	Ass AIC	ALC intake (weekly)	Unit	Ref BP mmHg	Ref BP gr	RIE BP mmHg	RIE BP gr
519	NO	30		137/63	normotensive	122/57	normotensive
520	YES	90				150/90	normotensive
521	YES	18		130/90	normotensive	110/70	normotensive
522	NO	10				120/60	normotensive

Number	Ref Na	Ref K	Ref Bic	Ref Bil	Ref ALP	Ref GGT	Ref H+	Ref Cr	Ref ALT	Ref PT
1	138	3.4	19				44	98	50	71.3
2	144	4.3		77	71	61		99	81	40.6
3	135	6.1	7	22	449	68	37.8	130	90	142
4	135	3.3	17	186	87			129	99	40
5	137	4.9	11				60.4		167	71
6	144	3.6	23					89	53	
7	135	3.9	4	77	394	129	72.5	138	124	
8	136	5.1	8	99	70		58	305	387	81.8
9	135	3		58	45	22		52	62	13.8
10	136	4.5	13	80	378	59		275	264	51.3
11	141	3.8	26	12	140			70	186	16
12	142	3	23	34	209	161		74	266	50
13	138	3.9		9	182	19	32	101	70	
14	141	3.3	20	976				83	336	36
15	145	4.6		76	102	26		174	93	54
16	128	3.2	21	3297	157			123	175	14
17	134	5.2		79	94	45	49	369	369	172
18	136	4.3	24	75	171				182	
19	136	4.7		65	72	46	53.7	179	216	35
20										
21	129	4.1	19	87	185	388	34	175	193	31
22	145	4.7	10	121	395	63	74	141	216	33
23	137	5	24					210	348	43
24	138	3.5		165	178			67	62	25
25	131	4.4	19	36	242	51	36	426	660	68
26	142	3.9		29	113		38	63	259	14
27	131	3.9	23.5	6880	114	194	32.8	92	83	35
28	141	3.2	18	47	193	11	37	110	91	35
29	136	3.7	23	116	92			116	286	14
30	135	4.9		103	253	33	37.8	340	304	50
31	144	4.9		123	237			161	120	58
32	136	4	17.3	76	219		36.5	80	52	25
33	142	4	22	54	92	44	31	50	56	15.3
34	129	4.5	20.9		188	219	40	394	544	
35	135	3.8	26	211	221	81		79	270	15
36	140	4.7	21	34	90	42	37	99	81	42
37	136	3.8		165	286	59			225	87
38	136	3.7	24	69	64	24	38	78	68	21
39	137	5		178	312	157	42	462	460	38
40	136	5.2	15	74	154		63	111	419	52
41	123	5.7					36	297	253	143
42	119	7.3	7	240	1910	850	81	339	362	101
43	141	4.1	21	6		38		84	400	13.8
44	14	4.9	16	45			37		116	20

Number	Ref Na	Ref K	Ref Bic	Ref Bil	Ref ALP	Ref GGT	Ref H+	Ref Cr	Ref ALT	Ref PT
45	139	4.6	24	39	284	44	41	57	93	27.2
46	140	4.1	21	75	599	64		79	73	
47	134	4.3	20	62	72	30	39	86	61	22.5
48	132	5.8	13				40.5	457	529	77
49	139	3.4		24	84	21		107	108	12
50	128	4.1		97	286	192		450	488	51
51	140	3.5	17	39	220		43	65	176	16
52	130	4.5	10	81	168	132	83	221	317	37.4
53	134	4	25	52	298	95		66	42	30
54	137	4.9		62	92	70		112	85	27
55	140	4	26.2	118	69	46	33.5	80	72	18.3
56	136	5.8		31	127	98	35	150	80	53
57	134	4.4		124	122	174		141	277	65
58	134	3.8	34	129	256	53	32	107	75	32
59	128	4.9	19	55	326			129	107	63
60	132	3.2	23	35	179	79	35	92	54	16
61	141	4.4	13				56.7	130	115	19
62	138	4.2	23				33.2	90	80	21
63	139	3.4	16	33	80	215	38	70	250	43
64	144	4.3	6.9	85	156		67	126	112	21.5
65	138	3.7	20	101	126	14	46.6	111	75	22
66	140	4.3		60	193	38		93	184	63
67	142	3.3	26	29	96		36	94	134	
68										
69	134	4.2	26	83	129	102		95	137	42
70	138	3.6	28	96	74	167	39		74	14
71	134	3.5	18	23	251	120	42	99	70	18.1
72	141	3.3	13.4				63.8	98	56	27.8
73	130	3.4		145	353	276		195	305	76.6
74	137	4	22	42	286	20	24.9	79	65	29.5
75	137	4.4	17	81	149	31	35.2	59	38	14
76									208	18
77	142	2.9	17	44	212	43		84	65	18
78	133	7.2	26	176	269	421		122	219	28
79	134	3.9	29	130	271		44.1	80	99	30
80	139	5	17	82	260	55	46	108	118	39
81	142	3.7	9		117		60	133	132	67
82				119	146		31	96	95	30
83	141	4	25	66	624	36		90	97	40
84	138	4.2		54	193	19		80	83	32
85	145	3.8	13.8					70	45	25
86	137	5.3	9	100	428	317	42	104	78	85
87	144	4.5		69	129	267	33	119	124	23.8
88	136	3.5	30	48	140	23	34	67	64	39
89	138	3.1	22.7	15	126	12	32	73	145	21
90	135	3.6		166	293	347		79	224	51
91	141	4	20.5	45	182	69		96	119	23
92	132	4.4		132	293	260	36.1	75	75	69
93	129	5.6		63	532	376	87.2		301	180
94	140	3.6		57	113	53		83	85	19.3
95	142			47	109	103		99	140	14.8

Number	Ref Na	Ref K	Ref Bic	Ref Bil	Ref ALP	Ref GGT	Ref H+	Ref Cr	Ref ALT	Ref PT
96	137	4.3	15	39		531	64.2	170	136	18
97	136	3.7	19	118	372	424	44	95	354	22
98	140		26	109	104			87	147	13
99	131	6.7	21.4		161		35	167	158	63
100	138	3	19.1	109	112	170	48.6	97	85	42.9
101	143	5		65	139	85	94.4	260	340	54.9
102	140	4.3	22	139	63	52	35.2	122	121	13
103	138	3.2		4	80	24	47.9	101	123	10
104	136	4.8	8	65	103	28	60	200	281	120
105	140	2.8	22	36	53			93	67	
106	134	5.1		139	631	315	58	573	507	50
107									298	
108									81	
109	141	3.8	20	47	80	61	50	99	71	27.8
110	129	6	18	154	354	192	37.9		547	
97	136	3.7	19	118	372	424	44	95	354	22
98	140		26	109	104			87	147	13
99	131	6.7	21.4		161		35	167	158	63
100	138	3	19.1	109	112	170	48.6	97	85	42.9
101	143	5		65	139	85	94.4	260	340	54.9
102	140	4.3	22	139	63	52	35.2	122	121	13
103	138	3.2		4	80	24	47.9	101	123	10
104	136	4.8	8	65	103	28	60	200	281	120
105	140	2.8	22	36	53			93	67	
106	134	5.1		139	631	315	58	573	507	50
107									298	
108									81	
109	141	3.8	20	47	80	61	50	99	71	27.8
110	129	6	18	154	354	192	37.9		547	
111	136	4.3	5	12	59		124		90	23
112	120	3.4	17	79	199			246	239	66
113	135	4.8		118	89	117		113	114	26
114	133	4.1	24	82	199	151	58	317		59.3
115	141	4.8		150	313	140	69.6		256	25
116	136	3.1		124	170		35.4	102	70	22
117	137	3.5	21	72	91	44	44	74	97	16.5
118	134	4.8	18	112	236		46	205	255	86.4
119	136	3.7	15				41.3	132	132	21
120	142	4.6	15	13	217		35.7	111	102	20
121	130	4.1	27	57	79	40		76	148	34
122	127	4.9		137	736	393		423	398	67
123	136	4.5	9	77			40	102	67	41
124	125	4.2	8	109	387	345	125	490	598	180
125	129	6.8	16	106	331			389	415	53
126	135	3.3		41	205	26		76	74	25.2
127	146		4	46	302	31	91	210	172	39
128	132	4.7		152	201	442		123	123	33
129	138	4.5	6	50	119	103	104	130	126	50
130	139	3.2		38	317	45		94	114	17
131	134	5	19	123		137		156	296	
132	133	2.8	25	17	334	113	38	80	148	30
133	145	3	18	91	49	79		68	103	30
134	144	3.8	25	70	94	180	36	120	274	30

Number	Ref Na	Ref K	Ref Bic	Ref Bil	Ref ALP	Ref GGT	Ref H+	Ref Cr	Ref ALT	Ref PT
135	146	5.5	3				134		416	103
136	134	3	16	61	21	220	42	55	159	25
137	140	2.9	14	80	134	235	40.6	116	112	28
138	135	3.4	21	14	158	21		95	22	14.8
139	136	3.9		189	172	139	41	207	125	
140	148	2.9	13	101	352		38.5	114	84	51
141		6.6	12.9				52.1	238	250	69
142	138	3	20	33	35	7	32	46	61	21
143	139	4.8	15.9	73	160	182	45	246	481	54
144	142	3.4	12.3	43	543		63	74	41	19
145	140	3.7		59	65		34	97	62	20
146	135		7	63	278	211	106.2	204	260	79.6
147	133	5.4	16	74	682	397	38	189	419	79
148	136		20	52	348		34	65	81	35
149	134	4.3	18	123	154	153		137	162	86.8
150	140	4.4	20		357		40.4	89	108	44
151	140	5		72	140		40	128	183	62
152	141	3.3	17		174	59	36	79	95	30
153	140	3.4		79	80			83	96	12.2
154	133	3.7		106	220	554	49.9	93	147	48
155	147	3.2	7					130	147	106
15	131	5.6		106	459		36.2	485	453	58
157	130	3.1		6	182	36		85		10
158	136	3.9	21		63	114	35	78	82	18.3
159	140	4.5	14	80	101	51	47	85	52	39
160	140	3.4	21	68	119	20	33.8	75	336	44
161	141	5.1	16	73		94	36	94	292	28
162	134	3.3							56	33.6
163	136	3.9	24				39.7	83	108	
164	130	4.6	23	130		264	47.2	459	381	56.8
165	131	4.5		116	145		43	130	107	39
166	135	3.4	24.9	26	136	113	35.8	282		43.9
167	141	4.7	28	96	309	115	35	105	106	
168									156	72
169	145	3.5	17	87	196	34	41	116	68	155
170	132	5.6		96	76	161	32	273	291	99
171	140	3.6	19				38.9	109	97	23
172	144	3.8					48		102	39
173	137	3.2		47	100	28		84	88	15
174	139	3.1	27	19	225	107	30	80	140	67
175	142	3.2	17	19	80			103	341	33.6
176	136	4.9	3.7	35	127	66	73.3	217	139	22
177	135	3.7		73	88	36		64	56	38
178	141	3.9		86	313		41	97	88	24.4
179	140	3.5		62	210	30		93	125	32
180	140	4.6		44	89	26		68	70	14
181	138	4.5	12		340		54	185	263	84
182	137	5.2	19	68	399	148	43.1	316	417	37.9
183	133	3.6	26	71	112	50	40.5	63	47	37
184	134	5.1		84	264	43	75.4	204	237	60
185	143	4.8	18	130	211	188	40.3	341	341	64.7
186	138						35.8	179	134	51
187	141	2.8	14	75	227		40.2	65	250	20

Number	Ref Na	Ref K	Ref Bic	Ref Bil	Ref ALP	Ref GGT	Ref H+	Ref Cr	Ref ALT	Ref PT
188	141	3.6	9	137	828	530		134	147	79
189	132	3.6					40	75	57	60
190	142	5	32	63	104		37	77	73	25
191	140	4.3	30	41	170		34.4	189	263	71
192	125	5.4		64	716			380	346	46.5
193	145	4.1	13	26	270			90	119	30
194	138		6	42	159			101	203	84
195	142	4.6	8	35	124		41	131	109	18
196	139	4	28	76	160	26		111		15
197	143	2.4		25	42	96	47	53	46	18.6
198	133	4.2		42	338			79	47	36
199	144	4.6	9	78	85	124	114	98	234	54.9
200	146	4.6	6				89	95	421	21
201	140	4.2		163	460	707	62.3	218	216	
202	141	3.4	18	61	233	69		80	17	30
203	140	3.9	19	86				75	285	63
204	135	4.7	18	58	107	290	63	359	367	41.7
205									117	
206	141	3.9	24	67	85	45	36	92	76	52
207	137	5.5	20	110	174		39	267	255	50
208	144	2.3	11	38	79	25	35	100	54	19.6
209	139	3.3	5.7	135	153	192	7.07	116	208	38.3
210	136	3.7	18.2	33	202		41.8	75	291	17
211	135	3.9	20		63	23	35	76	81	23.5
212	143	4.1		43	278			85	212	19
213	139	3.7	23	8	236	25		75	171	15
214	141	3.9		46	82	45	38	155	141	15
215	142	4					40	143	186	44
216	132	3.7	26	140	250			85	164	60
217	140	3.4		30	163		39.8	94	285	19
218	145	5.4	7		378	19	115	175	136	58
219	132	3.7		46	72	33	33.1	82	82	29
220	136	5.2	11	65	144	30	58.3	151	166	55
221				2086	137	137	44	169	95	90
222	137	5.4	8				159	181	216	50
223	144	4.6		53	146	45	43.9	124	208	48.4
224	134	4.5		180	136	180		105		
225	139	3.9	14				53	157	211	123
226	130	8.5	6					254	212	120
227	134	3.2	26	12	233		36.4	100	92	12.8
228	146	4.6	5.2	85	298		90	140	177	66
229	147	4.4	23	42	127	20	120	47	106	14
230	136	4.2	9	93	166			315	323	67
231	138	5.4					86		376	100
232				109			40	32	327	50.5
233	136	4.4	13	187	173			125	99	88
234	139	4.3	23	870	57	38	38	120	95	18
235	144	4	14	162	120			133	140	40
236	143	4.8	25	43	110	52		96	84	54
237	138	4.5		197	149			107	136	
238	134	5.2			333	420		142	271	25
239	137	3.9	18		262	97	36.2	102	73	24.9
240	136	3.3	14.7		241	284	50.9	504	1359	32.9

Number	Ref Na	Ref K	Ref Bic	Ref Bil	Ref ALP	Ref GGT	Ref H+	Ref Cr	Ref ALT	Ref PT
241	141	4.5		112	112	148	49	176	173	37
242									119	
243				48			40	360	340	64
244	138	4	28	112	1011	142		100	82	83.3
245	143	3.1	25		95			105	89	14
246	132	3.4		111	88			96	110	28
247	149	5.3	9				70.4	290	243	127
248	135	6.8		29	154	69	46	137	313	50
249	137	5.2		80	269	108	45	108	133	
250	141	5.1	14	119	70	24	75	189	250	87
251	141	3.4	21	58	2877	64		92	66	30.9
252	142	4.5	11	97	236	48	51	125	106	40.9
253	140	5.1		102	119	304	77.6	249	249	42
254	134	4.3	19	31	162	60		92	122	16.8
255	139	5.5	4	61	320	237	112	159	188	50
256	143	3.4		23	57	24		92	169	20
257	140	3.8	26.5	50	92			98	341	28.3
258	140	3.5	6		159		52	312	346	10
259	142	4.1	14	26	60	20		73	126	20.5
260	139	3.9	28	64	76	26		65	67	53.7
261	132	3.2	21	49	56	89	37	67	227	18.8
262	131	4.2	19				35	115	91	111
263	136	3.8	29	32	107		31	193	226	18
264									82	35
265	138	4.8	17	87	133	41	36	124	141	31.9
266	132	3.2		86	94	233	33.7	71	95	24.8
267	132	6.6	4.1	80	0	102		156	253	
268	139	3.8	18.7	127	115	314	41.7	209	281	70.3
269	137	4.9		120	438	70		71	76	136
270	137	3.3	21.4	48	119	26		84	66	165
271	132	4.2		104	152	0	40	293	347	63
272	123	4.4		170	210	202	38		361	45
273	137	5.5	14.8	60	267	29	44	85	90	44
274	126	3.7	29	89	180	303	31	571	548	73
275									78	26
276	136	4.7	8.1					292	214	
277	140	4.1	24	57	281		43	99	298	22.8
278	135		6	48			90	195	331	138
279	138	2.3	11	120	147		51		66	
280	139	4.7		96	273			225	329	79
281	144	4.1		30	460	47		77	41	21
282	140	4.3	18.4	100	93	56	39.92	10	67	35
283	137	4.1	30.9	210			29.2	730	644	77
284	137	3.5		108	124		36	87	86	26
285	144	4.1	8				95	220	245	120
286	142	4	28	29	116		44	95	105	21
287	130	4.6		173	130	307		238	229	112
288	137	2.2	28	155	196			107	109	20
289	132	5.1			157	35	42	104	73	85
290	138	4.7	26	115		110	40	76	90	56
291	136	3.1	21	19	75	118	37	108	95	
292	140	3.2		27	156		40	89	180	17
293	139	3.3	23		285	85	44	475	355	42

Number	Ref Na	Ref K	Ref Bic	Ref Bil	Ref ALP	Ref GGT	Ref H+	Ref Cr	Ref ALT	Ref PT
294	134	3.9	17	72	284	273	67	121	259	71
295	142	4.2	13	54		56	65	102	174	70
296	144	6.1		16	43		58	155	366	14
297	131	5.2	21	116	117	308	38	183	216	74.1
298	146	4.7		74	125	46	69	177	166	84
299	133	5	27				39	87	73	60
300	138	3.1	14	19	84	21	49	89	118	16.8
301	140	4.3		18				78	65	200
302	137	3.7	17		312	38	37	95	44	42
303	137	4.6	17.2	30	263	59	44.9	136	241	23.5
304	136	4.2	25	108	383	186		149	155	66
305	145	3.4	19					71		16.1
306	132	4.5	25	75	320	115		178	191	
307	133	4.5	19.4	23	86	15	45	79	75	42
308	136	6		129	141	89		99	96	71
309	139	3.8		90	91			84	194	16.1
310	133	4.2	34	69	122	168	34.6	160	128	22
311	140	3.7	22	58	97	50		62	69	32
312	138	3.6	24	60	56	52	38		172	25
313	141	4.1					39.6	70	57	31
314		2.7	23					80	50	23
315	137	3.8					36		86	60
316	136	5.1		81	117		47	177	232	64.4
317	135	4.6	12				80.8	113	128	16
318	140	3.4		57	182	13		74	48	21.9
319	134	5.6	18	111			42	95	123	100
320	139	4.4	29		210	396		558	594	40.8
321	139	4.4						179	231	65
322	126	4.6		62	1080	491	38	446	498	42.9
323	136	3.7	21	250	204			100	78	30
324	142	3.6		67			34.4	127	201	
325	134	5	19	127	158	45	36	121	84	88
326									136	
327										
328	137	4.7	11				59	121	92	108
329									182	
330										
331	138	3.8	20	75	54	68	39	84	74	22.9
332	135	3.9		44	193	61		78	90	17
333	138	4.5	23	66	317	113	40.9	137	390	34
334									56	
335	135	5.1	16	104	461	44	43	107	103	86.9
336	137	3.9	18	6	192	12	44	71	71	15
337								284	420	23
338	135	2.8			185	32		82	89	42
339	140	4.2		33	293	49		83	87	21.6
340	134	4.6	14	61	178		69	160	173	35
341	139	3.7	22	61	98		39	78	59	20
342									96	
343	135	5.3		84	136			151	278	50.8
344	128	3.8	21	98	690	153	45.9	75	73	78.8
345	139	3.9	17	54	334	76	66	99	109	
346	147	3.6	16	70	260	201	69	129	223	28.2

Number	Ref Na	Ref K	Ref Bic	Ref Bil	Ref ALP	Ref GGT	Ref H+	Ref Cr	Ref ALT	Ref PT
347	142	3.6	17	98	93	42	35	68	113	20.7
348	137	4.6	20	24000			58	203	281	79.2
349	145	3.6		76	136	56	120	207	246	36
350	128	6.6		129	406	424	38	448	359	60.7
351	140	3.8					39.3	97	236	61.6
352	142	3.7	17				45	43	70	20
353	132	5.4		103	119	137	34.7	111	86	30
354	142	4.2	13	46	207	455		138		28
355	137	4.5	19	89	275	341	49	154	176	36
356	141	3.2	16	97	351		42.7	75	91	20
357	132	6.2		93	102	245		192	215	37.3
358	140	4.1	18.6	239	239	210		110	137	
359	135	3.5	18.5	94	151	56	50	80	98	46.8
360	133	3.3		75	76	22	36.5	70	104	20.3
361									106	
362	139	4.6	19	78	178	71	36	108	74	77
363	137	6.7	20		425	182	34	401	439	34.3
364	141	3.8	13	31	255	9		37	36	20
365	137	4.6		192	135			494	535	104
366	136	6.9		120	482		36	249	248	34
367	135	4.1		53	76			63	81	18
368	127	6.1		65	259	146	70	138	138	112
369	137	5.5	12	127	311	632	45	258	315	34
370	133	3.7	17	26	545		59	140	165	52
371	129	6.3		41	605	171		477	419	52.2
372	131	5.1	14	134	309	231	39	190	157	46
373	133	4.3	31	79	128	175		118	555	19.8
374				9				120	149	30
375	139	4.4	28	21	92	12	29	66	92	13
376	147	3.7		15			48		87	18
377	138	4.4		92	278	155	43	403	454	38.4
378	140	3.5	20				48	81	58	15
379	141	3.4			171			82	207	17
380	130	4.1		140	163	332	47.6	444	452	40
381	140	3.4	25.5	47	52		35	77	65	21
382	133	4.1		104	195	314		226	303	14.5
383	141	4.4	21	129	192	290	41	104	197	35.5
384	139	5.7	7	64	543	239	144	126	219	34.6
385	140	4.6	12	23	314	26	43	129	284	21
386	139	5.1	19	142	224		38	128	196	28
387	138	3.1		93	283	51	41	47	79	35
388	140	5.9	4		262	54	98.1	111	260	78
389	143	4	21	54	240	67	35	83	129	28
390	143	4.6		5	98	50	33	101	107	48.4
391									394	
392	139	4.6	20	108	82	39	40	180	356	92.4
393	140	2.9		30	94	128	39	85	60	
394	136	3.8	17	12	45			79	61	23
395	141	3.8						75	186	86
396	127	4.9	8	29	246	155	78	74	130	24.8
397	144	5.3		82	118	82	100	255	270	
398									108	91.2
399	139	3.3	13	31	124	24	49	88	59	36.9

Number	Ref Na	Ref K	Ref Bic	Ref Bil	Ref ALP	Ref GGT	Ref H+	Ref Cr	Ref ALT	Ref PT
400	144	4.1	18	36			37	62	43	
401	138	4	19.3		100		47	178	161	32
402	138	4.3	22	105	125		38	105	70	56
403	137	3.5		33	101	18		107	118	19
404	138	3.6		133				250	203	36
405	134	5.8		79	472	671	79	453	470	89
406	138	4.4	19	19	3.5			100	421	51
407	143	3.5							61	26
408	145	4.8	12	40		26	37.6	100	105	32.6
409	131	4.3	17	177	350			79	163	39
410	137	3.5	24	97	423	206	37	63	56	19.8
411									340	
412	139	4.7			424			92	73	56
413	138	3.1	12	68				70	52	16.9
414	141	6.2	20	206	260	131		379	496	49
415									711	
416	133	3.3	19		248	24	52	77	76	24
417	136	4.3	19	172	512	91	33	193	170	57.9
418	134	3.5		69	84	163	37	91	461	45.2
419	139	3.8		52	189	334		99	233	27.1
420	143	4.4	13	122	428	198	69.2	124	118	29.4
421	144	6.3	4	63	102	51	67	240	215	24.6
422	134	4.3		30	174	232	38.1	254	318	23.5
423	133	4.9	25	99	593	47	38.8	84	80	44.1
424	133	3.6		44	181	292	46	90	83	12
425			22.3	64		404	38	116	174	19.3
526	132	4.5	23	104	139	98		86	95	44
427	137	3.8	16	67	84		38	90	89	25
428	136	4.8		125	162			85	71	56
429	136	4.8	20.3	79	151	343	41.8	80	146	35.3
430									234	
431	143	5.4		177	698	194	36	274	588	87
432	131	4.8	19	21	180	15	37.3	60	100	108
433	136	3.6	20.2	33	166	20	44	93	68	27.5
434	136	4.2		165	548	166	36	137	132	55
435	136	4.7	27	74	255	103		62	79	12
436	133	4.8	23	83	192	67	34	102	82	46.8
437	137	3.6	21	87	113	53	41	113	148	26
438	143	4.9	6					250	196	39
439	137	3.8	22	75		30			74	15.4
440	139	4.7	18	49	170		45	90	130	33
441			21	35	110		40		88	31
442	135	3.8		175	166	137		88	319	62
443	145	3.8	20	41	245	27	36	69	63	19
444	137	3.4	24	24	288	36	39	81	60	15
445	143	4.8							67	20
446	134	6.2			501	116	95.8	160	155	85
447	123	6	13				67	422	389	95
448	142	3.7	8.1	33	304	29	81	132	222	15.6
449	134	3.4	21.1		62	51	38.7	95	74	42
450	135	3.1		19	116	199	31.6	80	111	11
451	135	2.6	29	113	130	766		66	63	23
452	136	3.7		120	270	392		290	327	

Number	Ref Na	Ref K	Ref Bic	Ref Bil	Ref ALP	Ref GGT	Ref H+	Ref Cr	Ref ALT	Ref PT
453	139	2.9	19	15	96	17	33	99	87	24.8
454	143	3.3	23	30	202			98	208	
455	134	4.3	17.3	42	190	20		189	251	27.9
456	147		4				110	386	352	68
457	139	4.8	25.6	73	496	79	36	113	116	68
458	4			85	154	227		85	85	17
459	141	3.7	19	31	250	47	34	119	69	25
460	132	5.6		71	156	168		220	265	
461	140	3.7	20.4	86	90			91	85	25
462	138	4.1	19	55	115		37	134	93	18
463	134	3.6		11	276			95	100	100
464	134	5.8	12	277	733	126	41	1196	1212	18
465	136	4.8	22	59	326	22	35	111	116	40
466	137	4.6	18	48	131		41	95	67	26.4
467	136	5		182			70	130	163	45
468	135	4.1	25.6	146	313	181	37	72	80	110
469	145	2.3	14					122	74	21.7
470	141	4.5	9	92	139	83	76	179	179	55.2
471	139	6.9		104	121	226		109	164	21.9
472	134	3.3	24	42	82	78	34	98	75	17.4
473	145	4.3	10				76	122	109	25
474	136	3.6	21	36	78	26	37	164	181	41
475	128	4.2		125	501		54.6	118	78	58
476	143	4.2	30	56	201	26	32	106	240	22.7
477	129	3.6		125	174	124		416	432	49
478	140	3.7					34	88	68	21.5
479	133	3.3		111	120	139		75	82	16.2
480	135	5.6					166		197	60
481	139	3.3		102	106	327	37	149	31	38
482	141	3.3	15		56	26		101	83	28.8
483	142	4.8	14	29	60		76	223	256	
484	139	5.3		61	118			99	75	17
485	146	4.2	16					166	489	50
486	143	4.8	21	43	92		33	124	72	22
487	135	3.2	17	47	76	66	32	100	98	15
488	137	3.6	24	79	123		37	118	113	49
489	144	4		130	191	156	37.7	95	85	18
490	138	3.3		62	98	90		94	180	41
491	139	3.7	25	53	260	62	34	72	155	16
492	141	4	21	57	342	28		77	78	20
493	135	5.3		113	187	109		72	73	59
494	143	4.8	29	80	386		37	126	89	34
495	138	4.2	10.1	72	125	110	62	122	243	50
496	130	3.5	20	171	438	318	47.9	252	175	71
497	138	5.8	12	208	273	179		294	295	41
498	142	2.9	42	145	172			262	281	74
499	138	5	20	98	236	40	40	100	77	88
500	147	5.3	6	49	253	71	122	208	250	88
501	140	4.2		82	350	30		143	175	58
502	130	3.5	20		438	318	47.9	252	175	24
503									463	
504	138	4.6	20	96	445	165	36.6	99	213	38.3
505	140	3.8	25	95	126	337	33	118	98	28

Number	Ref Na	Ref K	Ref Bic	Ref Bil	Ref ALP	Ref GGT	Ref H+	Ref Cr	Ref ALT	Ref PT
506	140	3.3		92				84	218	23
496	130	3.5	20	171	438	318	47.9	252	175	71
497	138	5.8	12	208	273	179		294	295	41
498	142	2.9	42	145	172			262	281	74
499	138	5	20	98	236	40	40	100	77	88
500	147	5.3	6	49	253	71	122	208	250	88
501	140	4.2		82	350	30		143	175	58
502	130	3.5	20		438	318	47.9	252	175	24
503									463	
504	138	4.6	20	96	445	165	36.6	99	213	38.3
505	140	3.8	25	95	126	337	33	118	98	28
506	140	3.3		92				84	218	23
507	134	3.9		129	208	487	34.7	339	164	45
508	136	4.2		210	161	344		160	100	48.8
509	133	4.1	26	69	269	214		214	269	38
510	137	6.1		58			76.1	103	94	30.4
511	142	4.5	26	92	233	51		95	92	
512			17.8	105	127	132	43	132	177	42.8
513				165	135	391		55	52	60
514	141	3.7	17	48	267	58		110	83	23
515				173	99	46			83	33
516	140	3.3	24	57	97	101	37	68	221	39.5
517	142	2.2		28	177		66	123	84	18
518	143			48			44	90	76	24
519	139	2.9	17.7	32			46.7	84	145	77
520	134	4		57	343	130		120	72	45
521	142	2.9	19	42			60.8		113	22.2
522	144	3.6	16	26	96	30		49	56	18.8

Number	RIE APTT	RIE Na	RIE K	RIE Bil	RIE GGT	RIE ALP	RIE H+	RIE Bic	RIE Cr
1	46.9	137	2.6	134	76	188			50
2		144	3.6	79	62	98	30.1	25.5	81
3	68	149	2.9	78			38.5	23.8	90
4	48	134	3.2	205	214	87	39.3	20	99
5	85.5	133	5.8	107	42	46	57	13	167
6	51	137	4.2	114	39	178			53
7	63	127	3	62	100	62			124
8	164	136	4.4	94	78	130	97	6.3	387
9	48.6	129	3.6	97	56	83			62
10	57	126	4	101	59	192			264
11		127	4	112	156	115	30.3	25.8	186
12	70.9	133	4.2	146	139	185	41	22	266
13	50.7	126	6.9	64	107	50	7.07	5	70
14	47	134	3.9	50	148	111			336
15		143	5.2	46	17	57	39.6	26.7	93
16	34.3	130	3	78	336	182			175
17	80	134	5.2	79	45	94	49	15	369
18	54.1	128	3.6	69	101	82			182
19	77	138	3.9	64	50	69	37	16	216
20									
21	73	136	3.5	49	152	75			193

Number	RIE APTT	RIE Na	RIE K	RIE Bil	RIE GGT	RIE ALP	RIE H+	RIE Bic	RIE Cr
22	84.3	140	4.1	39	44	72	41.3	19	216
23	78.4	138	2.9	68	90	188	40.2		348
24	93	135	3.6	212	208	156	31.7	27.5	62
25	50.7	131	4.7	111	92	134	38.7	21.6	660
26	76.8	133	3.9	100	261	157	37.4	27.8	259
27	33.8	133	3.3	83	131	104			83
28	35	138	3	29	11	79			91
29	53	136	4.4	181	565	137	36.5	20.2	286
30	36.3	136	4	82	24	90	27.1	27.6	304
31	47.5	138	4.3	122	172	81	38	19	120
32	41	136	3	39	35	89	33	24	52
33	59.8	138	3.8	143	143	126	31	25.5	56
34	56.7	127	3.5	216	288	155	40.9	23.2	544
35	75	113	4.2	202	76	91	30.8	24	270
36		139	3.8	19	22	97			81
37	50	137	5.6	197	97	222			225
38	45	135	3.5	75	46	84	36	26	68
39	62	134	4.5	133	109	87			460
40	1	132	4.2	135	149	142	52.9	17.9	419
41	93	127	3.7	112	124	143	36.4	28.3	253
42	70.3	124	6.8	268	152	1018	103	9	362
43	46.3	133	3.9	74	493	158			400
44	60.3	140	3.9	106	68	119			116
45	4404	140	3.4	22	56	124	36	23	93
46	46	139	3.6	55	60	183			73
47	41	138	3.9	207	67	89	37	19	61
48	120	125	5.4	182	52	106	7.42	20	529
49	60	138	3.5	82	38	123	36.8	19	108
50	48	131	3.9	125	149	192	24.6	38.5	488
51	96.9	146	3.7	71	26	106	76	10.5	176
52	100	132	4.9	43	80	39	79.5	12.2	317
53	59.7	136	3.1	78	73	148			42
54	73	132	3.7	104	77	103	37.9	20.4	85
55	43.1	139	3.4	68	26	70			72
56	58	135	4.2	36	93	103	32	25.2	80
57		125	3.3	127	187	110			277
58	38	137	3.4	81	78	83			75
59	49	134	4.2	86	28	144	35.4	22.3	107
60	56.3	140	3.5	63	106	99	33	25	54
61		138	2.9	92	79	140	29	25	115
62	443	140	3.8	96	39	110	32	22	80
63	34.3	138	3	68	230	119	37	19.5	250
64		130	3.2	192	84	157	36	19	112
65	34.9	140	3.3	101	25	61	38	21	75
66	66	127	3.8	57	28	63	41	16	184
67	48	133	4	37	28	118	7.47	27	134
68									
69	56.2	137	3.2	112	106	189			137
70	42.4	134	4.1	58	145	94			74
71		136	4	141	98	188	36	23	70
72		134	4.2	57	27	91			56
73	59	129	3.7	136	104	78	32	27.5	305
74		137	3	39	25	108	33.3	26.3	65

Number	RIE APTT	RIE Na	RIE K	RIE Bil	RIE GGT	RIE ALP	RIE H+	RIE Bic	RIE Cr
75	74.5	139	3.2	90	50	94			38
76	47	130	3.8	108	39	144		21	208
77	60	132	3.9	103		141			65
78	50	131	4.1	94	174	47	36	24	219
79	46	131	3.2	149	79	146	35	27	99
80	41	137	3.7	56	54	103			118
81	43.5	141	3.8	117	24	26	41	.	132
82	57	137	3.1	129	224	195	32.3	24.7	95
83	37	134	3.4	58	35	240			97
84	42	141	3.4	39	32	92			83
85	46	135	3.9	76	47	67			45
86	44	133	3.5	99	290	132			78
87	72	128	3	90	296	132	30	27.8	124
88	45.3	143	4.1	83	38	145	31.2		64
89		140	2.9	67	27	81	32		145
90	60	138	3.3	145	190	77	41.2	23.7	224
91	72.4	137	3.8	58	104	99	39.2	17.9	119
92	53	127	4.2	107	222	101			75
93	170	125	5.4	79	169	87	51	13	301
94	41.5	136	3.5	68	59	146	34	29	85
95	43.1	132	3.1	117	199	124			140
96	120	132	3	31	47	92	57.1		136
97	79	124	2.9	137	400	139	43		354
98	60	146	3.5	93	93	65	27.5	30.3	147
99	46	129	5.9	87	90	120			158
100	57.6	131	4	118	110	100	34.3	22.4	85
101	114	134	4.4	42	56	107	49.2	15.7	340
102	55.1	136	3.7	182	58	90			121
103		132	4.7	144	85	137	33.4	23.8	123
104		129	5.3	66	14	79	53	15.8	281
105	43	138	4	94	20	96			67
106	76	139	4.9	85	159	129	135.1	5.8	507
107		135	4.8	94	293	150	141.7	6.9	298
108	55	135	3.5	7	297	190			81
109		139	3.8	114	59	130			71
110	62	130	4.1	134	123	88	51		547
111	63	145	3.7	19	25	34	38.6	18.1	90
112	70	124	4.1	49	308	162	70.3		239
113	64	135	5.2	147	168	103	41.3	7.97	114
114									
115	41	133	4.2	176	119	94	38.9	18.9	256
116	50	138	4	177	237	107	37	23	70
117	48	138	4.1	98	39	127			97
118	58	127	3.2	109	165	194	38.3	23	255
119	34	139	3.7	88	63	128	38.1	20	132
120	45.1	137	3.2	32	39	137	38	24.5	102
121		125	2.8	30	38	71	37	23	148
122	59	132	4.8	168	391	302			398
123	622	131	3.9	77	48	52		20	67
124	84	130	5.1	94	115	162	129.7	6.9	598
125	58	132	5.5	106	72	107		19.8	415
126		142	3.9	28	33	137	36	26.7	74
127	62	139	5.2	88	19		48.3	16.3	172

Number	RIE APTT	RIE Na	RIE K	RIE Bil	RIE GGT	RIE ALP	RIE H+	RIE Bic	RIE Cr
128	43	132	4.7	152	443	201	38.9	22.4	123
129	54	132	5.4	83	98	140	37.9	21.3	126
130	48	134	4.9	80	73	314	36	20	114
131	66	139	5.9	76	58	49	95	8	296
132		136	4.2	94	228	167			148
133	31.3	134	3.6	91	96	70			103
134	56	137	2.7	84	166	121	36.9	25.2	274
135	74	138	5.7	81	232	229	85.6		416
136	40.3	134	4.8	81	213	110	41	17	159
137	46.8	135	3.3	122	186	112	39	11	112
138	59			12126	86	37			22
139	51	134	4	170	114	121	38.5	21.7	125
140	2.5	135	4.2	113	107	172	36.7	23.5	84
141	46.7	134	6.4	78	54	109			250
142	54	134	3.1	68	14	74			61
143	105	135	4.2	122	64	76			481
144	28.6	134	3.9	36	48	55	48	19.5	41
145	38.9	140	3.3	47	49	128	37	21	62
146	51	135	4.7	58	119	152	56.1	15.8	260
147	102	140	4.2	104	229	147	45.3	19.5	419
148	46	137	3	38	32	129			81
149	66.4	129	2.5	124	172	141	31	32	162
150	63.8	135	4.1	124	55	135	37.7	19.2	108
151	57.1	136	4.9	63	43	141	40	23.5	183
152		134	3.7	79	61	74	33	20	95
153	55	134	3.3	90	96	80	28.1	24.4	96
154	58	131	4	69	390	92	85.9	10.7	147
155	43	134	3.2	18	41	56	7.27	5	147
15	55	133	4.4	76	342	109	60.3	14.4	453
157									
158	38.5	133	3	92	212	82	33	23	82
159	54.8	138	3.5	100	26	96	37	26	52
160	46	139	4.2	78	37	74	36	23.8	336
161	57.3	134	3.4	116	101	170	32	31.4	292
162	49	132	3.1	46	383	124			56
163	69	139	3.9	42	67	74	34.5	26.1	108
164	54	124	3.5	111	240	132	35.8	24.3	381
165	51	133	3.5	93	39	112	29	21	107
166	45.6	132	3.1	65	96	112			
167	43	141	4.3	105	111	107			106
168	4.8	139	4.5	79	56	113	41.6	17.1	156
169	43.7	142	3.6	105	39	125	32	25.5	68
170	89	129	4.7	105	72	162	44	17	291
171	42	142	3.6	55	47	74	34.7	26.5	97
172	47	138	3.3	99	75	93	34	28.6	102
173	210	141	3	200	62	143	35	27.1	88
174	40	142	3.7	98	202	106	32	29	140
175	108	137	3.9	55	28	86	62	18	341
176	63	134	4.1	92	81	131	35.7	20.1	139
177		131	3.7	47	86	140	32	18	56
178	50	139	3.9	132	196	110			88
179	55.6	141	3.4	117	38	134	37	20.5	125
180		140	4.1	92	54	126			70

Number	RIE APTT	RIE Na	RIE K	RIE Bil	RIE GGT	RIE ALP	RIE H+	RIE Bic	RIE Cr
181	65.2	138	4.5	60	35	127	87.3	16.5	263
182	43	137	5.1	55	159	169			417
183		140	3.7	100	36	108			47
184	90	133	5	62	32	107	77.1	13.3	237
185	50	140	4.1	87	97	128	33.7	30.3	341
186	63	141	3	82	35	109	25	21	134
187	210	138	3.3	98	51	69	52.4	17.9	250
188	59	138	3.5	145	252	138		.	147
189	47.8	137	3.3	84	79	145			57
190	41	135	3.5	51	270	110			73
191	51.8	139	3.9	44	11	41	32.1	32.1	263
192	74	119	4.8	73	493	234	69.8	12.3	346
193	63	138	6.2	61	27	138	41		119
194	200	128	5.1	69	210	159	58.8	16	203
195	50.7	136	4	55	104	120	45	22	109
196		130	3.6	104	87	204			
197		141	3.8	61	42	96	31	13	46
198	49	132	4.4	53	60	149			47
199	145	136	3.2				37	15.8	234
200	154	142	6.1	99	182	60	54.7	10	421
201	112	130	4	60	239	195	139.3	4.5	216
202	38	136	4.1	77	79	89			17
203	86.8	128	4	75	48	184	38.5	25	285
204	52.8	131	4.5	83	325	125	45	19	367
205	56	129	4.1	103	499	237			117
206	45.5	142	3.9	48	40	73		34	76
207	41.3	134	5.5	85	103	153	36	27	255
208	58	140	4.4	71	37	211	31.4	18.4	54
209	68	138	4.9	96	82	66	26.1		208
210	240	129	3.7	73	31	114	49.3	21.3	291
211	47.4	139	3.7	84	30	104			81
212	34	139	4.7	140	169	210	35.6	24.1	212
213	39	135	3.6	25	77	125	34	23	171
214	60	137	5.2	35	36	48	38	22.7	141
215	66.4	134	3	96	35	89	38		186
216		130	4	162	39	118			164
217	57	134	3.3	63	194	117			285
218	55.6	137	4.8	39	13	83	54.5	15.9	136
219	41	133	3.7	41	35	61	33.1	21.6	82
220	73	134	5.1	44	17	92	66.1	12.9	166
221		135	2.9	107	119	94	30	30.5	95
222	138.3	137	5.1	101	35	33	7.37	16.1	216
223	50	136	3.4	59	95	161	33	3.2	208
224		133	4.5	183	195	119			
225	98	129	4.4	84	128	171	32.8	23.2	211
226	200	135	7.3	79	46	79	106	4.7	212
227	41.5	127	3.2	119	21	118			92
228	74	134	5.9	85	20	194	67.4	10	177
229	43	141	4.3	105	111	107			106
230	78	137	3.9	45	85	32			323
231	47	138	5.4	79	53	178	40.8	12.7	376
232	47	129	2.8	117	348	126			327
233	62	136	5.5	166	27	48	33.2	12.7	99

RIE APTT	RIE Na	RIE K	RIE Bil	RIE GGT	RIE ALP	RIE H+	RIE Bic	RIE Cr	
234	50.6	138	3.5	190	50	143	35		95
235	47	135	4.1	198		172	4.1	20	140
236							27.7	19	84
237	66	129	4.6	161	49	126	63.2	11.3	136
238	53	134	4.5	149	216	129	34	26	271
239	40.3	141	3.3	22	97	112			73
240	37.3	126	3.8	371	378	336	47	18	1359
241	61	136	4.1	110	139	98	42.8	16.1	173
242	41	137	4.2	115	102	146	47.4	15.2	119
243	92.6	128	3.3	42	42	77	40	21	340
244	70.3	138	4	106	107	271	33	28	82
245	56	136	3.7	160	74	94	36	25	89
246	69	129	4	129	231	112	42.8		110
247	72.8	146	3.8	36	8	63	66	12.3	243
248	71	133	5.2	36	76	165			313
249	60	136	4	75	74	81	36.8	21.7	133
250	74	133	4.3	106	27	94	44.6	16.4	250
251	40.9	138	3	35	73	159			66
252	51.7	141	4.2	69	45	65	44	15	106
253	49	140	5.1	102	304	119			249
254	45	133	3.9	121	135	98	35	25	122
255	63	125	5.8	63	194	115	94		188
256	42	136	3.8	47	83	123	34	20	169
257	44.8	129	3.8	84	108	165			341
258	81	131	3.2	81	69	96	38	20	346
259	63.8	132	3.7	26	24	65	38	17	126
260	36	137	4.5	121	57	103	24	26.3	67
261		132	3.8	66	109	98			227
262	59.8	136	3.8	87	29	127	32	27	91
263		132	3	44	143	122	33	27	226
264	81	132	4.2	68	32	113			82
265	53.1	139	3.3	118	33	187	26.2	30.8	141
266	66	135	3.6	136	183	91	30.7	28.4	95
267	109	123	6.2	77	37	80	7.38	16	253
268	67	135	3.4	85	96	54	.	.	281
269		132	3.7	104	47	14			76
270	44.2	140	3.2	24	69	61	35	24.5	66
271	75.1	132	4.2	198	104	62	33.4	14.4	347
272	90	132	3.6	151	149	172	35.3		361
273	40	134	4.3	61	28	91	39.8	19.6	90
274	52.7	120	3				53	18.5	548
275	56.3	139	3.3	82	149	296	32.9	22.6	78
276	240	131	4.1	34	61	60	96.2	12.6	214
277	81.2	140	5.1	119	46	113			298
278	74	137	4.4	47	68	106	.	.	331
279	50.6	138	3.3	171	84	167			66
280	110	136	4.9	53	33	68	43.7	19.5	329
281	46	136	4.1	32	38	364			41
282	33.3	137	3.7	60	29	91			67
283	200	134	3.1	139	107	96	24	34	644
284	49.8	132	3	61	27	69			86
285	55.4	134	4.1	52	247	75	81	11	245
286	200	138	3.8	89	92	106	34.4	15.4	105

Number	RIE APTT	RIE Na	RIE K	RIE Bil	RIE GGT	RIE ALP	RIE H+	RIE Bic	RIE Cr
287	69	128	4.1	169	300	118	35	19.7	229
288	56	136	3.2	229	723	79			109
289	86.8	137	3.7	78	35	121	45.3	14.2	73
290	54	137	4.4	116	132	118	35.5	24.3	90
291	31	136	3.4	116	192	90			95
292	75	137	3.5	139	109	99	40	15	180
293	46.1	140	3	58	57	93	36		355
294	94	138	4.6	38	140	85	119	7.5	259
295	50.7	130	6.3	57	84	50	44.1	20.1	174
296	73	143	5.3	13	33	55	50.4	17.9	366
297	75.1	126	3.9	94	232	11			216
298	83.9	138	4.1	51	46	21			166
299	55.6	134	3.9	121	48	202	35	28	73
300	41.8	134	3	19	36	114			118
301	30	137	4	16	20	56	.	.	65
302	44	134	3.5	31	31	30	35	22.5	44
303	37	137	3.4	43	59	148	37	24	241
304	56	135	4.1	113	205	163			155
305									
306		132	3.6	70	83	114	34.9	23.3	191
307	62	137	3.7	37	47	101			75
308		137	5.3	116	51	131			96
309	55	137	3.8	81	100	111			194
310	50	134	3.4	64	140	90	30.3	34.4	128
311	60	137	3.9	42	65	99	36	21	69
312		136	2.7	76	167	73			172
313	44.5	139	4	34	19	74	7.54	22	57
314	36	134	2.2	43	65	130			50
315	39	137	2.5	80	49	113	33	18.5	86
316	62	130	4.8	100	150	147	35	25	232
317	42	135	4.3	157	109	202			128
318	47	139	3.6	56	28	108			48
319	62	126	6.3	86	33	84	42	17	123
320	40.5	157	4.5	161	262	142	32	28	594
321	45	141	5.1	57	67	199	65.7	18	231
322	60.8	121	4.5	69	308	132	57	20	498
323	44	135	2.7	341	544	87			78
324	54	137	3.6	128	322	132			201
325	70.5	135	3.7	117	38	149	34	24	84
326		127	3	161	228	174		36	136
327									
328	42.1	137	3.7	106	65	97	34	21	92
329	54	125		170	209	188	34	22	182
330									
331	44.8	137	3.2	100	109	107			74
332	57.2	137	4.2	113	191	122			90
333	68	138	4.2	74	145	124	40.4	21.2	390
334	48.8	135	3.9	86	34	554	39	22.5	56
335	9	127	4.1	72	31	134	32	26.9	103
336		136	3.9	24	40	90			71
337	50	132	3.9	118	138	95	35	26	420
338		135	3.1	72	23	89	37	23	89

Number	RIE APTT	RIE Na	RIE K	RIE Bil	RIE GGT	RIE ALP	RIE H+	RIE Bic	RIE Cr
339	38	141	3.8	29	52	140			87
340	67	139	4.2	96	79	124	62.4	14.2	173
341	44.3	138	3.4	61	31	140			59
342	56	142	4.1	98	73	206			96
343	53	134	3.4	79	200	114			278
344	85	129	4	132	166	235	42.2	19.5	73
345	74	138	4	58	69	149	56	3.6	109
346	67	137	4.7	108	218	115	51.6	9.8	223
347	63	132	3	135	30	155	35	25	113
348	62.6	126	5.9	79	73	94	29.6	25	281
349		162	4.1	46	30	73	151	4.2	246
350	48	127	4.4	118	259	120	48	23.5	359
351	2.2	4		11746	171	43			236
352	63.8	141	3.3	65	46	93	38	18	70
353	57	86	3.1	101	130	97	34.3	27	86
354	92	138	4.4				120	6.4	
355	44.8	129	3.5	95	265	96	38	21	176
356	49	133	4.1	179	89	159			91
357	61	126	4.3	100	207	82			215
358	49	144	3	392	104	162			137
359	72	139	4.1	92	47	181	31.6	19.5	98
360	45	135	3	70	26	81			104
361	57	139	3.8	86	99	99			106
362	47	136	3.3	56	65	110	36	19	74
363	120	138	4	167	96	97			439
364	40	130	3.1	53	26	114			36
365	91	124	4.7	208	232	73	58.2	5.8	535
366	43.2	133	4.5	100	317	131			248
367		133	3.4	69	87	114			81
368	155	127	6.1	65	146	259	70	8.4	138
369	39	137	4.8	131	501	125	48.8	17.7	315
370	71.4	132	3.7	42	125	307	7.4	22	165
371	46	128	5.4	43	176	221			419
372	51	132	3.6	107	203	107	39	18.7	157
373	37.8	127	3.2	58	139	108			555
374	46.3	134	3.6	35	16	107			149
375	52.2	130	3.3	88	27	164	24	25	92
376	30	138	3.5	31	25	204	39.6	21.3	87
377	45	137	4.4	78	96	83			454
378	33	133	4.3	63	23	119	39	18.5	58
379	55.6	136	3.1	131	718	106	40	24.5	207
380	50	125	4.5	137	306	149	57.3	16.8	452
381	30.6	137	3.2	44	207	91			65
382	64.6	125	5	125	212	97	41	20	303
383	49.3	138	3.7	137	303	102			197
384	115	136	6.4	59	126	159	105.2	8.2	219
385	115	139	5.2	55	21	123	45.7	13	284
386	44	130	4.4	130	95	186			196
387	43	138	4	93	106	171			79
388	103	127		87	46	67	67.5	13.9	260
389	45.9	136	4.3	74	97	102			129
390	57	133	3.7	91	95	162			107
391	42	136	4.8	111	60	111	39.5	24.3	394

Number	RIE APTT	RIE Na	RIE K	RIE Bil	RIE GGT	RIE ALP	RIE H+	RIE Bic	RIE Cr
392	43	136	3.8	97	40	91	21	26	356
393		135	3	76	127	158			60
394	61.1	136	3	77	16	103	34		61
395	52	137	4	133	26	143	41	21	186
396	45	134	4.1	42	162	104	40.4		130
397	120	139	5.2	53	119	97	118	4	270
398	48	132		62	248	91			108
399	40.6	137	3.2	31	23	52			59
400	43.4	135	3.5	72	85	136			43
401		140	3.9	68	45	93			161
402	70.7	136	3.7	75	49	93	25.7		70
403	58	136	2.9	74	59	114			118
404	104	135	3.5	85	63	83			203
405	78.9	136	4.2	68	196	126	76.4	11.7	470
406	33	136	3.1	21	73	116			421
407	44	136	3.4	52	48	127	33	18	61
408		132	4.1	56	35	106	38.3	23.2	105
409	60	130	4.4	176	255	135	35.1		163
410	53	137	3.7	128	176	217	34.6	26.8	56
411	51	128	4	99	89	75			340
412		137	3.5	30	31	92			73
413	54	137	3	84	165	240			52
414	44	136	4.6	169	75	181		2.56	496
415		128	3.1	38	66	84	44.8	18	711
416	56	136	3.3	81	47	124	22	18.5	76
417		135	3.8	197	65	211			170
418	57.6	132	3.6	98	208	114			461
419	56	135	3.6	112	268	227	34.7		233
420	53	138	4.8	107	182	127	45.1	14.1	118
421	74	138	3.5	57	40	72	37	16.5	215
422	43	127	4.1	27	198	164			318
423	67.9	130	4.2	93	44	210	44.6	27.1	80
424	34	132	3.7	56	232	170	46	.	83
425	56	137	3.5	133	320	134	36	23.6	174
526	6	131	3.9	108	112	156	38.8	22.3	95
427	37	134	3.2	86	36	84	38.8	21.4	89
428	48.4	137	4.4	126	68	139			71
429	48.3	133	3.2	45	187	85			146
430	122	149	3.8	54	192	69			234
431	101	126	5.2	158	162	100			588
432	51	135	3.5	68	66	120			100
433		136	4.1	95	48	95			68
434	77	132	3.4	122	116	205	33	28.5	132
435	45	136	3.8	68	103	249	31	27	79
436	37	137	3	47	94	92	30.7	25.8	82
437		138	4.3	81	54	68	38	24	148
438	70	137	5.5	77	51	20		7.4	196
439	52	137	3	82	28	108	35.9		74
440	39	140	5	93	41	86	47	13.8	130
441	53	137	3.8	42	44	133			88
442	67	135	4.3	175	193	180	36.1	22.8	319
443	74.1	138	3.6	59	17	122	7.43	24	63
444		142	3.3	118	114	178			60

Number	RIE APTT	RIE Na	RIE K	RIE Bil	RIE GGT	RIE ALP	RIE H+	RIE Bic	RIE Cr
445		135	3.6	77	43	122	32	34	67
446	94	141	5.1	28	45	91	112.4		155
447	105	126	5.1	53	39	62	104.4	10.7	389
448	200	142	4.4	33	20	89	122		222
449	48.9	127	3.1	20	60	53			74
450	53	133	3.4	190	571	274			111
451	47	134	2.9	102	778	117			63
452	42.5	131	3.2	124	582	239			327
453		142	3.9	31	22	60			87
454	45	135	3.7	97	160	113			208
455	53	135	5	85	34	115	34.9		251
456	256	128	5.3	59	50	111	66.1	16.7	352
457		140	4.4	69	51	225			116
458	42	1		85	154	227			85
459	44.3	137	2.6	48	29	114			69
460	82	131	4.2	73	90	99			265
461	43	138	2.8	55	29	81	35	25	85
462	46.4	147	3.9	126	10	38			93
463	56	140	4.1	125	215	144	33	23	100
464	38.2	132	5.1	245	200	323	47.2	21.3	1212
465	34	137	3.2	45	37	167			116
466		138	3.3	70	163	138			67
467	76	134	5.5	98	92	69	70.3	13.7	163
468	81.3	134	3.4	161	163	130			80
469		138	4.1	53	32	96			74
470	49.1	141	4.5	92	83	139	76	5	179
471	240	128	4.7	66	88	26	51.6	14.9	164
472	57.6	134	3	109	125	132	35	18.5	75
473	50.3	136	5.4	110	56	48	49	6	109
474	30.4	140	2.9	28	41	93			181
475	62	124	4.1	108	404	176	49.8	15.4	78
476	56	128	2.8	112	34	102	25		240
477	76.6	129	2.8	101	86	109	25.1	26.4	432
478		141	3.5	39	32	115	34	29	68
479	61	132	4.2	105	82	118	33.3	23.3	82
480	110	135	5.6	68	41	100	139		197
481	40	139	3	261	346	102	30	27	31
482		139	4.2	117	25	92	31	25	83
483	108	143	3.8	24	24	72	77.6	16	256
484	53	135	3.4	94	72	156			75
485	110	129	4.6	81	29	90	41	22.1	489
486	44.5	139	3.6	29	61	131			72
487	51.4	134	3.9	96	145	114			98
488		137	3.4	71	146	91	31.7	25.6	113
489	46	134	3.7	113	167	94			85
490	62	135	3.3	93	185	121	32	26	180
491	61.2	136	3.9	105	99	162			155
492	42	140	3.6	52	29	129			78
493	61.9	135	4	145	125	189	32	27	73
494	43.2	131	3.4	83	49	167			89
495	73.7	131	6.3	72	22	89			243
496	46.5	132	2.9	230	297	162	28.8	25.6	175
497	64	131	3.9	195	194	98			295

Number	RIE APTT	RIE Na	RIE K	RIE Bil	RIE GGT	RIE ALP	RIE H+	RIE Bic	RIE Cr
498		133	2.8	120	135	98		44	281
499	67.5	137	3.2	60	29	69	28		77
500	135	140	6.1	26	27	75	71		250
501	38.8	141	5.2	70	26	175	46	13	175
502	56.7	132	2.9	230	297	162	28.8	25.6	175
503		128	6.3	192	180	133	70	10.5	463
504	38.3	130	4.5	76	235	256			213
505	41	142	5	90	309	113	44.7	23.9	98
506	53	134	3.3	67	119	101	36.7	24	218
507	38	133	2.8	129	441	149	33.6	21.1	164
508	35.3	135	3.1	244	348	169			100
509	52.3	118	2.9	89	180	122	31	24	269
510	40	140	4.7	99	85	125			94
511	53	138	3.3	73	28	83		30.7	92
512	56.1	137	5.3	97	76	92	43	17.8	177
513	38	131	3.6	182	672	150	35	25	52
514	44	133	2.7	57	49	137	35	22	83
515		136	2.7	187	50	112			83
516	35.5	135	3	71	108	97			221
517	65	136	4.5	91	76	142			84
518	45	134	3.5	56	114	90	36.1	24.6	76
519	58.5	131	4.9	125	187	142	46	19	145
520	43	131	3.2	50	180	152			72
521		127	3.8	139	50	98	36.2	19.3	113
522		139	4.2	131	90	179			56

No	RIE ALT	RIE PT	High PT inn	High PT man	Dialysis	Survival	REF 8gr according to PT and Cr
1	10000	59.4		59.4		survived	refpt>=25, refcr<=120
2	17741	42			not required	survived	refpt>=25, refcr<=120
3		38		56	not required	Died	refpt>=25, refCr>120, <=180
4	5834	95.1			dialysis required	Died	refpt>=25, refCr>120, <=180
5	18000	107		107	dialysis required	Died	refpt>=25, refcr<=120
6	10739	50.1		66.99	not required	survived	
7	2546	97		195	dialysis required	Died	
8	3662	205		205	not required	Died	refpt>=25, refcr>=300
9	8329	52.2		78.5	not required	survived	refpt<25, refcr<=120
10	12506	42	51.3	90	dialysis required	survived	refpt>=25, refcr>180, <300
11	8173	17.3		21.4	not required	survived	refpt<25, refcr<=120
12	6586	85		110	not required	survived	refpt>=25, refcr<=120
13	3994	40.6			dialysis required	Died	
14	7480	68		115	not required	survived	refpt>=25, refcr<=120
15	1027	59.3		59.3	not required	survived	refpt>=25, refCr>120, <=180
16	6805	32.3		32.3	not required	survived	refpt<25, refcr>120, <=180
17	13670	116			dialysis required	survived	refpt>=25, refcr>=300
18	14750	40.3		40.3	not required	survived	
19	12910	70	72	144	dialysis required	Died	refpt>=25, refCr>120, <=180
20				15	not required	Died	
21	1576	20			dialysis required	Died	refpt>=25, refCr>120, <=180

Number	RIE ALT	RIE PT	High PT inn	High PT man	Dialysis	Survival	REF 8gr according to PT and Cr
22	3644	162			dialysis required	survived	refpt>=25, refCr>120, <=180
23	10595	120		200	dialysis required	Died	refpt>=25, refcr>180, <300
24	9009		40		not required	survived	refpt>=25, refcr<=120
25	11210	29.4			dialysis required	Died	refpt>=25, refcr>=300
26	8434	72.1		93	not required	survived	refpt<25, refcr<=120
27	7810	25.5		25.5	not required	survived	refpt>=25, refcr<=120
28	748	26		37	not required	survived	refpt>=25, refcr<=120
29	9776	49		49	not required	survived	refpt<25, refcr<=120
30	10988	24.3		50	not required	survived	refpt>=25, refcr>=300
31	17000	63.3		63.3	not required	survived	refpt>=25, refCr>120, <=180
32	2381	29		31	not required	survived	refpt>=25, refcr<=120
33	5492	75.6		99.5	not required	survived	refpt<25, refcr<=120
34	3774	30.9		35	dialysis required	Died	.
35	16400	65		65	dialysis required	Died	refpt<25, refcr<=120
36	14276	57.3		57.3	not required	survived	refpt>=25, refcr<=120
37	17920	31	87	130	not required	survived	refpt>=25, refcr<=120
38	12906	44		80	not required	survived	refpt<25, refcr<=120
39	5077	44			dialysis required	survived	refpt>=25, refcr>=300
40	4320	32	52	63	dialysis required	survived	refpt>=25, refcr<=120
41	6063	185			not required	survived	refpt>=25, refcr>180, <300
42	2473	31.5			dialysis required	Died	refpt>=25, refcr>=300
43	9713	26.5		59	not required	survived	refpt<25, refcr<=120
44	13405	80.8		125	not required	survived	
45	10994	20.2		82	not required	survived	refpt>=25, refcr<=120
46	8300	27	27	49	not required	survived	
47	8790	23			not required	survived	refpt<25, refcr<=120
48	3270	50			dialysis required	Died	refpt>=25, refcr>=300
49	3114	59	130		dialysis required	Died	refpt<25, refcr<=120
50	2735	18			dialysis required	Died	refpt>=25, refcr>=300
51	8628	205			dialysis required	Died	refpt<25, refcr<=120
52	3916	61	61	130	dialysis required	Died	refpt>=25, refcr>180, <300
53	9090	89.4	89.4		not required	survived	refpt>=25, refcr<=120
54	2969	74		83	not required	survived	refpt>=25, refcr<=120
55	9797	27.8	67		not required	survived	refpt<25, refcr<=120
56	8964	31		50	not required	survived	refpt>=25, refCr>120, <=180
57	9590	89		89	not required	survived	refpt>=25, refCr>120, <=180
58	5902	16	32	22	not required	survived	refpt>=25, refcr<=120
59	9276	46			not required	survived	refpt>=25, refCr>120, <=180
60	6500	40.4		43.4	not required	survived	refpt<25, refcr<=120
61	9756			49.4	not required	survived	refpt<25, refcr>120, <=180
62	3740	36	56		not required	survived	refpt<25, refcr<=120
63	10000	31.9			not required	survived	refpt>=25, refcr<=120
64	11320	62			not required	Died	refpt<25, refcr>120, <=180
65	1133			91	not required	survived	refpt<25, refcr<=120
66	6192	120		120	dialysis required	Died	refpt>=25, refcr<=120
67	8649	33		35	not required	survived	
68					dialysis required	Died	
69	6467	55.5		58.9	not required	survived	refpt>=25, refcr<=120

Number	RIE ALT	RIE PT	High PT inn	High PT man	Dialysis	Survival	REF 8gr according to PT and Cr
70	9016	36.1	36.1		not required	survived	.
71	10000	85.8	89.3		not required	survived	refpt<25, refcr<=120
72	2147	39.3		53.5	not required	survived	refpt>=25, refcr<=120
73	6949	33		76.6	dialysis required	Died	refpt>=25, refcr>180, <300
74	9494	24	45	71	not required	survived	refpt>=25, refcr<=120
75	9945	50.2		50.2	not required	survived	refpt<25, refcr<=120
76	9586	67		67	not required	survived	.
77	10560	76	76	130	not required	survived	refpt<25, refcr<=120
78	1091	58		79	dialysis required	survived	refpt>=25, refCr>120, <=180
79	13560	15	30		not required	survived	refpt>=25, refcr<=120
80	17255	54		54	not required	survived	refpt>=25, refcr<=120
81	12240	98.5	142		dialysis required	Died	refpt>=25, refCr>120, <=180
82	11140	49	49	87	not required	survived	refpt>=25, refcr<=120
83	9596	45	45	70	not required	survived	refpt>=25, refcr<=120
84	8292	36	36	68	not required	survived	refpt>=25, refcr<=120
85	4080	45	90		not required	survived	refpt>=25, refcr<=120
86	1182	37	85	71	not required	survived	refpt>=25, refcr<=120
87	8499	36	39	61	not required	survived	refpt<25, refcr<=120
88	18289	65.8	65.8		not required	survived	refpt>=25, refcr<=120
89	9440	52		90	not required	survived	refpt<25, refcr<=120
90	1767	39		58	not required	survived	refpt>=25, refcr<=120
91	10490	66.3	86.3		not required	survived	refpt<25, refcr<=120
92	5739	51	69	90	not required	survived	refpt>=25, refcr<=120
93	1079	157		157	dialysis required	Died	refpt>=25, refcr<=120
94	6749	37.3		37.3	not required	survived	refpt<25, refcr<=120
95	9872	41.4	41.4		not required	survived	refpt<25, refcr<=120
96	844	72		130	not required	Died	refpt<25, refcr>120, <=180
97	3673	41	47		dialysis required	Died	refpt<25, refcr<=120
98	4453	18			not required	survived	refpt<25, refcr<=120
99	12010	33		43.9	not required	survived	refpt>=25, refCr>120, <=180
100	6981	59.4		116	dialysis required	survived	refpt>=25, refcr<=120
101	5303	84.9			dialysis required	Died	refpt>=25, refcr>180, <300
102	16852	66.6	66.6		not required	survived	refpt<25, refcr>120, <=180
103	5136	46	120		not required	survived	refpt<25, refcr<=120
104	10000	120		120	dialysis required	Died	refpt>=25, refcr>180, <300
105	10969	33			not required	survived	
106	5091	56	56	153	dialysis required	Died	refpt>=25, refcr>=300
107	7742	37	37		not required	Died	
108	2325	35		48	not required	survived	
109	10000	61.3		61.3	not required	survived	refpt>=25, refcr<=120
110	6481	40	40	64	dialysis required	survived	
111	311	25	55	120	not required	survived	
112	2190	31	66		not required	Died	refpt>=25, refcr>180, <300
113	11520	71	71	71	dialysis required	Died	refpt>=25, refcr<=120
114					not required	Died	refpt>=25, refcr>=300
115	2918	31	87	80	dialysis required	Died	refpt>=25, refcr<=120
116	8782	29		29.8	not required	survived	refpt<25, refcr<=120
117	25298	69		71.5	dialysis required	survived	refpt<25, refcr<=120

Number	RIE ALT	RIE PT	High PT inn	High PT man	Dialysis	Survival	REF 8gr according to PT and Cr
118	5520	54		67	dialysis required	Died	refpt>=25, refcr>180, <300
119	760	33	103	180	dialysis required	Died	refpt<25, refcr>120, <=180
120	16000	54.6		107	not required	survived	refpt<25, refcr<=120
121	8359	48		48	not required	survived	refpt>=25, refcr<=120
122	2236	44			not required	survived	refpt>=25, refcr>=300
123	4447	49			dialysis required	Died	refpt>=25, refcr<=120
124	4757	118		118	not required	Died	refpt>=25, refcr>=300
125	14806	34	53		dialysis required	survived	refpt>=25, refcr>=300
126	9400	60.6		60.6	not required	survived	refpt>=25, refcr<=120
127	9891	77	200		dialysis required	Died	refpt>=25, refcr>180, <300
128	11751	33	33	42.5	not required	survived	refpt>=25, refCr>120, <=180
129	4795	41		41	dialysis required	survived	refpt>=25, refCr>120, <=180
130	12800	73.8		100	not required	survived	refpt<25, refcr<=120
131	6825	26	45		dialysis required	Died	
132	12370	42.8		64	not required	survived	refpt>=25, refcr<=120
133	9180	49		72	not required	survived	refpt>=25, refcr<=120
134	10130	31		89.7	dialysis required	Died	refpt>=25, refcr<=120
135	7059	38	103		dialysis required	Died	refpt>=25, refcr<=120
136	3700	48.8		48.8	not required	survived	refpt>=25, refcr<=120
137	301	27.8			not required	Died	refpt>=25, refcr<=120
138		24	24	40	not required	survived	refpt<25, refcr<=120
139	4166	30	31	71	not required	survived	
140	13680	43	53	102	not required	survived	refpt>=25, refcr<=120
141	10000	53	69		not required	survived	refpt>=25, refcr>180, <300
142	1260	42	60	130	not required	survived	refpt<25, refcr<=120
143	4177	37.6	72.9		not required	Died	refpt>=25, refcr>180, <300
144	889	27		112	not required	survived	refpt<25, refcr<=120
145	7933	35.7		74	not required	survived	refpt<25, refcr<=120
146	6623	30			dialysis required	Died	refpt>=25, refcr>180, <300
147	2938	63		117	dialysis required	Died	refpt>=25, refcr>180, <300
148	8809	28			not required	survived	refpt>=25, refcr<=120
149	4373	60.8		86.8	not required	survived	refpt>=25, refCr>120, <=180
150	10000	97.3		120	not required	survived	refpt>=25, refcr<=120
151	10000	59		77	not required	survived	refpt>=25, refCr>120, <=180
152	8770	55.3		55.3	not required	survived	refpt>=25, refcr<=120
153	6754	42	52		not required	survived	refpt<25, refcr<=120
154	1318	29	48	53	not required	Died	refpt>=25, refcr<=120
155	5856	49			dialysis required	Died	refpt>=25, refCr>120, <=180
15	1362	42	77		not required	Died	refpt>=25, refcr>=300
157			74		not required	survived	refpt<25, refcr<=120
158	10130	32.3	32.3		not required	survived	refpt<25, refcr<=120
159	4563	24			not required	survived	refpt>=25, refcr<=120
160	8604	57.8			not required	Died	refpt>=25, refcr<=120
161	10000	71.8	72		dialysis required	survived	refpt>=25, refcr<=120
162	2966	39		39	not required	survived	refpt>=25, refcr<=120
163	1628	29	57		not required	survived	
164	2605	41			not required	survived	refpt>=25, refcr>=300
165	10000	99			not required	survived	refpt>=25, refCr>120, <=180

Number	RIE ALT	RIE PT	High PT inn	High PT man	Dialysis	Survival	REF 8gr according to PT and Cr
166	10000	38.4		43.9	not required	survived	refpt>=25, refcr>180, <300
167	7154	48		63	not required	survived	
168	8060	51	72	99	not required	survived	refpt>=25, refcr<=120
169	7430	32.8		176	not required	survived	refpt>=25, refcr<=120
170	5315	93			not required	survived	refpt>=25, refcr>180, <300
171	10140	35	35	66	not required	survived	refpt<25, refcr<=120
172	8780	51		75.1	not required	survived	refpt>=25, refcr<=120
173	4458	120		180	not required	survived	refpt<25, refcr<=120
174	5447	39	67		not required	survived	refpt>=25, refcr<=120
175	8330	240		240	dialysis required	survived	refpt>=25, refcr<=120
176	12280	54			dialysis required	Died	refpt<25, refcr>180, <300
177	10330	33.9		99	not required	survived	refpt>=25, refcr<=120
178	7397	43			not required	survived	refpt<25, refcr<=120
179	9056	85.4		89.6	not required	survived	refpt>=25, refcr<=120
180	13631	57	74		not required	survived	refpt<25, refcr<=120
181	3510	38.6		38.6	not required	Died	refpt>=25, refcr>180, <300
182	7906	22.2		22.2	not required	survived	refpt>=25, refcr>=300
183	3050	48		62.8	not required	survived	refpt>=25, refcr<=120
184	5551	228	300	300	dialysis required	Died	refpt>=25, refcr>180, <300
185	7051	23	64.7	74	dialysis required	survived	refpt>=25, refcr>=300
186	10294	51	91		not required	survived	refpt>=25, refCr>120, <=180
187	1668	180		180	dialysis required	survived	refpt<25, refcr<=120
188	2898	79			dialysis required	Died	refpt>=25, refCr>120, <=180
189	17190	42.3		42.3	not required	survived	refpt>=25, refcr<=120
190	6543	20		20	not required	survived	refpt>=25, refcr<=120
191	15400	64.4		71	not required	survived	refpt>=25, refcr>180, <300
192	1549	51	200		dialysis required	Died	refpt>=25, refcr>=300
193	10675	104			dialysis required	survived	refpt>=25, refcr<=120
194	4300	120		180	not required	Died	refpt>=25, refcr<=120
195	3583	68.7		141	not required	survived	refpt<25, refcr>120, <=180
196		42			not required	survived	refpt<25, refcr<=120
197	3820	53		80	not required	survived	refpt<25, refcr<=120
198	7282	16	36		not required	survived	refpt>=25, refcr<=120
199		150		150	not required	Died	refpt>=25, refcr<=120
200	8085	150		150	dialysis required	Died	refpt<25, refcr<=120
201	1497	106	106		dialysis required	Died	
202	7301	31			not required	survived	refpt>=25, refcr<=120
203	5630	50.6			dialysis required	Died	refpt>=25, refcr<=120
204	3452	48.1		48.1	not required	survived	refpt>=25, refcr>=300
205	3260	25	25	37	not required	survived	
206	4319	70.5		70.5	not required	survived	refpt>=25, refcr<=120
207	8022	34.3		50	not required	survived	refpt>=25, refcr>180, <300
208	7661	107			dialysis required	survived	refpt<25, refcr<=120
209	5491	31		1	dialysis required	survived	refpt>=25, refcr<=120
210	12136	240		240	dialysis required	survived	refpt<25, refcr<=120
211	5005	73.8		123	not required	survived	refpt<25, refcr<=120
212	6558	25			not required	survived	refpt<25, refcr<=120
213		25			dialysis required	survived	refpt<25, refcr<=120

Number	RIE ALT	RIE PT	High PT inn	High PT man	Dialysis	Survival	REF 8gr according to PT and Cr
214	1563	31	91	77	not required	survived	refpt<25, refcr>120, <=180
215	17500	99			dialysis required	survived	refpt>=25, refCr>120, <=180
216	10000	54	60		dialysis required	survived	refpt>=25, refcr<=120
217	10890	78		81	not required	survived	refpt<25, refcr<=120
218	2149	97.1		135	not required	Died	refpt>=25, refCr>120, <=180
219	17400	25	29	55	not required	survived	refpt>=25, refcr<=120
220	6998	91	130	210	dialysis required	Died	refpt>=25, refCr>120, <=180
221	6547	52.3		52.3	not required	survived	refpt>=25, refCr>120, <=180
222	4444	74.4			dialysis required	Died	refpt>=25, refcr>180, <300
223	6383	51	51	107	dialysis required	Died	refpt>=25, refCr>120, <=180
224	10455	33	33	54	not required	survived	
225	11820	105	200		dialysis required	Died	refpt>=25, refCr>120, <=180
226	8500	200		200	dialysis required	Died	refpt>=25, refcr>180, <300
227	4583	41.5		55.4	not required	survived	refpt<25, refcr<=120
228	4989	67			dialysis required	survived	refpt>=25, refCr>120, <=180
229	7154	48		63	not required	survived	refpt<25, refcr<=120
230	2219	41			dialysis required	Died	refpt>=25, refcr>=300
231	5795	100		100	dialysis required	Died	refpt>=25, refcr<=120
232	3456	40	50.5	57	not required	survived	refpt>=25, refcr<=120
233	10000	40		120	dialysis required	survived	refpt>=25, refCr>120, <=180
234	29790	68.4		68.4	not required	survived	refpt<25, refcr<=120
235	5867	56			dialysis required	survived	refpt>=25, refCr>120, <=180
236		52		52	not required	survived	refpt>=25, refcr<=120
237	15200	120	120		not required	survived	
238	10965	36		36	not required	survived	refpt>=25, refCr>120, <=180
239	15645	32.8	33		not required	survived	refpt<25, refcr<=120
240	1038	14.7		14.7	dialysis required	survived	refpt>=25, refcr>=300
241	2956	56	116	140	not required	Died	refpt>=25, refCr>120, <=180
242	4434	32	64	92	not required	survived	
243	4360	64.1		99	not required	survived	refpt>=25, refcr>=300
244	6159	64.6		64.6	not required	survived	refpt>=25, refcr<=120
245	3931	46	81		not required	survived	refpt<25, refcr<=120
246	10200	66	109	201	dialysis required	survived	refpt>=25, refcr<=120
247	4992	118		118	dialysis required	Died	refpt>=25, refcr>180, <300
248	7811	40	50	70	dialysis required	survived	refpt>=25, refCr>120, <=180
249	14840	50			dialysis required	survived	
250	12680	115		115	dialysis required	survived	refpt>=25, refcr>180, <300
251	12910	34.6		34.6	not required	survived	refpt>=25, refcr<=120
252	5823	45.1		48.4	not required	survived	refpt>=25, refCr>120, <=180
253		42	42		not required	Died	refpt>=25, refcr>180, <300
254	9788	49.3		76	not required	survived	refpt<25, refcr<=120
255	4237	42			dialysis required	Died	refpt>=25, refCr>120, <=180
256	15085	38		83	not required	survived	refpt<25, refcr<=120
257	6340	34.6		34.6	dialysis required	survived	refpt>=25, refcr<=120
258	6620	78		78	dialysis required	survived	refpt<25, refCr>=300
259	8508	59.3	59.3		not required	survived	refpt<25, refcr<=120
260	6680	65		66	not required	survived	refpt>=25, refcr<=120
261	12592	26	26	0	not required	survived	refpt<25, refcr<=120

Number	RIE ALT	RIE PT	High PT inn	High PT man	Dialysis	Survival	REF 8gr according to PT and Cr
262	8229	88.2		88.2	not required	survived	refpt>=25, refcr<=120
263	8800	24.9		43	not required	survived	refpt<25, refcr>180, <300
264	10000	65.3		92	not required	survived	refpt>=25, refcr<=120
265	10000	62.8		149	dialysis required	Died	refpt>=25, refCr>120, <=180
266	8846	28	33	74	not required	survived	refpt<25, refcr<=120
267	9784	62			dialysis required	survived	
268	1170	24			dialysis required	Died	refpt>=25, refcr>180, <300
269	5463	200		200	not required	Died	refpt>=25, refcr<=120
270	9510	23.8		23.8	not required	survived	refpt>=25, refcr<=120
271	838	57	63		dialysis required	Died	refpt>=25, refcr>180, <300
272	3079	51	65	0	dialysis required	Died	refpt>=25, refcr<=120
273	11600	38			dialysis required	Died	refpt>=25, refcr<=120
274	418	40.5			not required	Died	refpt>=25, refcr>=300
275	6807	62.5	124		not required	survived	refpt>=25, refcr<=120
276	5439	135			dialysis required	Died	
277	9788	125			dialysis required	survived	refpt<25, refcr<=120
278	7009	30			dialysis required	Died	refpt>=25, refcr>180, <300
279	2501	53.4		118	not required	survived	
280	10000	71			dialysis required	survived	refpt>=25, refcr>180, <300
281	910	34		34	not required	survived	refpt<25, refcr<=120
282	14990	35.8	75		not required	survived	refpt>=25, refcr<=120
283	5968	54.9	77		dialysis required	survived	refpt>=25, refcr>=300
284	13775	48.3		48.3	dialysis required	survived	refpt>=25, refcr<=120
285	3039	34			dialysis required	Died	refpt>=25, refcr>180, <300
286	16200	42		51.3	dialysis required	survived	refpt<25, refcr<=120
287	2105	59		84	not required	Died	refpt>=25, refcr>180, <300
288	2123	27	27	28	not required	survived	refpt<25, refcr<=120
289	6783	143		159	not required	survived	refpt>=25, refcr<=120
290	11153	50	67	110	not required	survived	refpt>=25, refcr<=120
291	1226	21	34	33	not required	survived	
292	12170	58	58	110	dialysis required	survived	refpt<25, refcr<=120
293	9472	30.8		45	not required	survived	refpt>=25, refcr>=300
294	4625	74	74		not required	Died	refpt>=25, refCr>120, <=180
295	10000	54.4			dialysis required	Died	refpt>=25, refcr<=120
296	7941	26	27	63	dialysis required	survived	refpt<25, refcr>120, <=180
297	10000	53.3	74.1		not required	survived	refpt>=25, refcr>180, <300
298	5944	97.5		100	dialysis required	Died	refpt>=25, refCr>120, <=180
299	13360	76.9		76.9	not required	survived	refpt>=25, refcr<=120
300	9174	44.3		44.3	not required	survived	refpt<25, refcr<=120
301					not required	survived	refpt>=25, refcr<=120
302	10540	69		149	not required	Died	refpt>=25, refcr<=120
303	11731	31	78		not required	survived	refpt<25, refcr>120, <=180
304	8770	41	66		not required	survived	refpt>=25, refCr>120, <=180
305				83	dialysis required	Died	refpt<25, refcr<=120
306	9736	52		95	dialysis required	Died	
307	7545	63		63	not required	survived	refpt>=25, refcr<=120
308	10000	62.1		62.1	not required	survived	refpt>=25, refcr<=120
309	11280	51		66	not required	survived	refpt<25, refcr<=120

Number	RIE ALT	RIE PT	High PT inn	High PT man	Dialysis	Survival	REF 8gr according to PT and Cr
310	7184	27	29	37	not required	survived	refpt<25, refcr>120, <=180
311	11390	47		72.4	not required	survived	refpt>=25, refcr<=120
312		56		56	dialysis required	survived	refpt>=25, refcr<=120
313	13564	22.2		22.2	not required	survived	refpt>=25, refcr<=120
314		25	25		not required	survived	refpt<25, refcr<=120
315	5012	30		30	not required	survived	refpt>=25, refcr<=120
316	15920	54		114	dialysis required	survived	refpt>=25, refCr>120, <=180
317	11700	49		54	not required	survived	refpt<25, refcr<=120
318	3306	36	48.6		not required	survived	refpt<25, refcr<=120
319	12395	110		111	dialysis required	Died	refpt>=25, refcr<=120
320	3034	41.5			dialysis required	Died	refpt>=25, refcr>=300
321	3230	63		81	not required	Died	refpt>=25, refCr>120, <=180
322	1446	40.1			dialysis required	Died	refpt>=25, refcr>=300
323	6094	40		48	not required	survived	refpt>=25, refcr<=120
324	6816	40		114	dialysis required	survived	
325	5279	63			not required	Died	refpt>=25, refCr>120, <=180
326	4503	32.7		32.7	not required	survived	
327					.	Died	
328	761	78		78	not required	survived	refpt>=25, refCr>120, <=180
329	4964	58			dialysis required	Died	
330					not required	Died	
331	11935	58.3		58.3	not required	survived	refpt<25, refcr<=120
332	7161	62.7		62.7	not required	survived	refpt<25, refcr<=120
333	11500	35		73	dialysis required	survived	refpt>=25, refCr>120, <=180
334	9407	67		100	not required	survived	
335	7968	63	86.9	111	not required	survived	refpt>=25, refcr<=120
336	8575	18	18		not required	survived	refpt<25, refcr<=120
337	10910	37		59	not required	survived	refpt<25, refcr>180, <300
338	6000	64.2	64.2		not required	survived	refpt>=25, refcr<=120
339	7582	23		23	not required	survived	refpt<25, refcr<=120
340	4725	102		102	dialysis required	Died	refpt>=25, refCr>120, <=180
341	8231	36.3	50		not required	survived	refpt<25, refcr<=120
342	15665	80		108	dialysis required	Died	
343	5837	23			dialysis required	survived	refpt>=25, refCr>120, <=180
344	1689	64	78.8		not required	survived	refpt>=25, refcr<=120
345	5092	57	115		dialysis required	Died	
346	8765	74	117	162	dialysis required	Died	refpt>=25, refCr>120, <=180
347	13000	120			dialysis required	survived	refpt<25, refcr<=120
348	10000	88.9		92	dialysis required	Died	refpt>=25, refcr>180, <300
349	4051	44	44		dialysis required	Died	refpt>=25, refcr>180, <300
350	1827	18	60.7	28	dialysis required	Died	refpt>=25, refcr>=300
351		61		130	not required	survived	refpt>=25, refcr<=120
352	6500	43			dialysis required	survived	refpt<25, refcr<=120
353	10640	35	35	63	not required	survived	refpt>=25, refcr<=120
354		59		59	dialysis required	Died	refpt>=25, refCr>120, <=180
355	13080	92.8			dialysis required	survived	refpt>=25, refCr>120, <=180
356	8611	51			not required	survived	refpt<25, refcr<=120
357	2948	40	66	121	dialysis required	Died	refpt>=25, refcr>180, <300

Number	RIE ALT	RIE PT	High PT inn	High PT man	Dialysis	Survival	REF 8gr according to PT and Cr
358	1635	37		37	not required	survived	
359	5449	81		81	not required	Died	refpt>=25, refcr<=120
360	5292	25	25	5.7	not required	survived	refpt<25, refcr<=120
361	7010	40		81	not required	survived	
362	1062	66		80.3	not required	survived	refpt>=25, refcr<=120
363	4770	48.7		80.1	dialysis required	Died	refpt>=25, refcr>=300
364	3619	27	49		not required	survived	refpt<25, refcr<=120
365	13380	111	111		dialysis required	Died	refpt>=25, refcr>=300
366	4420	38.1	38.1		not required	survived	refpt>=25, refcr>180, <300
367	8745	26	27		not required	survived	refpt<25, refcr<=120
368	3686	112	135		dialysis required	Died	refpt>=25, refCr>120, <=180
369	10450	28	34	48	not required	survived	refpt>=25, refcr>180, <300
370	992	29.8			dialysis required	Died	refpt>=25, refCr>120, <=180
371	2036	39	200	95	dialysis required	Died	refpt>=25, refcr>=300
372	5980	46.3			not required	survived	refpt>=25, refcr>180, <300
373	5573	15.9	19.8		not required	survived	refpt<25, refcr<=120
374	7208	34.6		34.6	not required	survived	refpt>=25, refcr<=120
375	12675	83.4		89.8	not required	survived	refpt<25, refcr<=120
376	625	18	29	36	not required	survived	
377		23		23	not required	survived	refpt>=25, refcr>=300
378	492	21		33	not required	survived	refpt<25, refcr<=120
379	5380	57		57.3	not required	survived	refpt<25, refcr<=120
380	9197	39			dialysis required	Died	refpt>=25, refcr>=300
381	13000	33		53	not required	survived	refpt<25, refcr<=120
382	1940	55.3		56.2	dialysis required	survived	refpt<25, refcr>180, <300
383	10000	43.8		43.8	not required	survived	refpt>=25, refcr<=120
384	8286	48	200	200	dialysis required	Died	refpt>=25, refCr>120, <=180
385	6163	120	120		dialysis required	Died	refpt<25, refcr>120, <=180
386	12488	40	40	73	not required	survived	refpt>=25, refCr>120, <=180
387	7562	67			not required	survived	refpt>=25, refcr<=120
388	7927	35	78		dialysis required	Died	refpt>=25, refcr<=120
389	10785	60	60		not required	survived	refpt>=25, refcr<=120
390	12684	48	48.4	83	not required	survived	refpt>=25, refcr<=120
391	9891	36			dialysis required	survived	
392	10580	69.6		69.6	dialysis required	survived	refpt>=25, refCr>120, <=180
393	13520	69	69	126	not required	survived	
394	9000	63.7		63.7	not required	survived	refpt<25, refcr<=120
395	11305	64		64	not required	survived	refpt>=25, refcr<=120
396	5925	29		62	not required	survived	refpt<25, refcr<=120
397	12465	101			dialysis required	Died	
398	8298	36	91.2	72	not required	survived	refpt>=25, refcr<=120
399	183	34.5	36.9		not required	survived	refpt>=25, refcr<=120
400	4768	50	50		not required	survived	
401	1146	33		41.7	not required	survived	refpt>=25, refCr>120, <=180
402	8770	35		66	not required	survived	refpt>=25, refcr<=120
403	7796	37	57	67	.	survived	refpt<25, refcr<=120
404	3135	52	57	155	dialysis required	Died	refpt>=25, refcr>180, <300
405	4538	110			dialysis required	survived	refpt>=25, refcr>=300

Number	RIE ALT	RIE PT	High PT inn	High PT man	Dialysis	Survival	REF 8gr according to PT and Cr
406	6730	15		15	not required	survived	refpt>=25, refcr<=120
407	10000	42		66	not required	survived	refpt>=25, refcr<=120
408	15600	55	130	104	dialysis required	Died	refpt>=25, refcr<=120
409	2870	106		108	not required	Died	refpt>=25, refcr<=120
410	13175	47		47	not required	survived	refpt<25, refcr<=120
411	11783	20			dialysis required	Died	
412	10000	27.9		56	not required	survived	refpt>=25, refcr<=120
413	10000	56.6		65	not required	survived	refpt<25, refcr<=120
414	10000	25		25	not required	survived	refpt>=25, refcr>=300
415	122	28.8			not required	Died	
416	11520	41	61		not required	survived	refpt<25, refcr<=120
417	14358	74.5		87	not required	survived	refpt>=25, refcr>180, <300
418	13715	46.8		46.8	dialysis required	survived	refpt>=25, refcr<=120
419	3080	90.4		90.4	dialysis required	survived	refpt>=25, refcr<=120
420	5444	28			dialysis required	Died	refpt>=25, refCr>120, <=180
421	8454	54			dialysis required	survived	refpt<25, refcr>180, <300
422	4372	13	23.5		not required	survived	refpt<25, refcr>180, <300
423	5383	53		93	dialysis required	survived	refpt>=25, refcr<=120
424	1526	9	12	16	not required	survived	refpt<25, refcr<=120
425	1600	42		79	dialysis required	survived	refpt<25, refcr<=120
526	11480	49	200	117	dialysis required	survived	refpt>=25, refcr<=120
427	2143	31		120	dialysis required	survived	refpt>=25, refcr<=120
428	8177	35.8		35.8	not required	survived	refpt>=25, refcr<=120
429	10000	51	56.4		dialysis required	survived	refpt>=25, refcr<=120
430	2949	55			dialysis required	Died	
431	8675	73.2		73.2	dialysis required	survived	refpt>=25, refcr>180, <300
432	14305	39	108		not required	survived	refpt>=25, refcr<=120
433	14380	57.4		57.4	not required	survived	refpt>=25, refcr<=120
434	13800	41	55	54	not required	survived	refpt>=25, refCr>120, <=180
435	9617	33		33	not required	survived	refpt<25, refcr<=120
436	11076	20	46.8	38	not required	survived	refpt>=25, refcr<=120
437	2418	19		30.9	not required	survived	refpt>=25, refcr<=120
438	6154	48	48		dialysis required	Died	refpt>=25, refcr>180, <300
439	9840	42		81	not required	survived	
440	2542	39		82	dialysis required	Died	refpt>=25, refcr<=120
441	7508	46		92	not required	survived	refpt>=25, refcr<=120
442	9625	57		61	dialysis required	Died	refpt>=25, refcr<=120
443	8299	74.2	78.8		not required	survived	refpt<25, refcr<=120
444	13350	67.2			not required	survived	refpt<25, refcr<=120
445	14365	42		42	not required	survived	
446	694	85	98	130	dialysis required	survived	refpt>=25, refCr>120, <=180
447	4287	34			dialysis required	Died	refpt>=25, refcr>=300
448	1463	200		200	not required	Died	refpt<25, refcr>120, <=180
449	4113	35.3	50		not required	survived	refpt>=25, refcr<=120
450	5422	45	45	65	not required	survived	refpt<25, refcr<=120
451	1000	19	23	27	not required	survived	refpt<25, refcr<=120
452	5357	47.5		54.5	not required	survived	
453	11490	34.3		46	not required	survived	refpt<25, refcr<=120

Number	RIE ALT	RIE PT	High PT inn	High PT man	Dialysis	Survival	REF 8gr according to PT and Cr
454	10000	19		19	not required	survived	
455	14440	56			dialysis required	survived	refpt>=25, refcr>180, <300
456	6641	200			dialysis required	Died	refpt>=25, refcr>=300
457	12700	53.3		53.3	not required	survived	refpt>=25, refcr<=120
458	7611	17	17	26	not required	survived	refpt<25, refcr<=120
459	10000	55	55		not required	survived	refpt>=25, refcr<=120
460	3156	73			dialysis required	Died	
461	10000	34		65	not required	survived	refpt>=25, refcr<=120
462	45	18.5		19.5	not required	survived	refpt<25, refcr>120, <=180
463	7565	33		113	not required	Died	refpt>=25, refcr<=120
464	831	14.3			dialysis required	Died	refpt<25, refCr>=300
465	5335	22	40	34	not required	survived	refpt>=25, refcr<=120
466	10000	43		43	not required	survived	refpt>=25, refcr<=120
467	5991	86		130	not required	Died	refpt>=25, refCr>120, <=180
468	7430	73.3		73.3	not required	survived	refpt>=25, refcr<=120
469	10000	65			not required	survived	refpt<25, refcr>120, <=180
470	3014	55.2		200	dialysis required	Died	refpt>=25, refCr>120, <=180
471	6236	240		240	dialysis required	Died	refpt<25, refcr<=120
472	2569	58.8		106	dialysis required	survived	refpt<25, refcr<=120
473	8112	42.6		200	dialysis required	Died	refpt>=25, refCr>120, <=180
474	10000	21			not required	survived	refpt>=25, refCr>120, <=180
475	1975	53	58	94	not required	survived	refpt>=25, refcr<=120
476	10930	73		130	dialysis required	survived	refpt<25, refcr<=120
477	4677	56.7		56	not required	survived	refpt>=25, refcr>=300
478	2370	45.8		62	not required	survived	refpt<25, refcr<=120
479	8224	67		95	not required	survived	refpt<25, refcr<=120
480	7050	167			dialysis required	Died	refpt>=25, refcr<=120
481	3443	22			not required	survived	refpt>=25, refCr>120, <=180
482	7172	70		71	not required	survived	refpt>=25, refcr<=120
483	3756	85.9			dialysis required	Died	
484	18700	32	54	85	not required	survived	refpt<25, refcr<=120
485	10000	69.6			dialysis required	Died	refpt>=25, refCr>120, <=180
486	9756	26.2	26.2		not required	survived	refpt<25, refcr>120, <=180
487	15200	53.5		53.5	not required	survived	refpt<25, refcr<=120
488	4619	43		63	not required	Died	refpt>=25, refcr<=120
489	8646	31		47	not required	survived	refpt<25, refcr<=120
490	6254	28		41	.	survived	refpt>=25, refcr<=120
491	15460	100		100	not required	survived	refpt<25, refcr<=120
492	1909	25		50	not required	survived	refpt<25, refcr<=120
493	18600	95.3		101	not required	survived	refpt>=25, refcr<=120
494	10000	57.8		64	not required	survived	refpt>=25, refCr>120, <=180
495	7138	155		190	dialysis required	Died	refpt>=25, refCr>120, <=180
496	1333	19.8		72	not required	survived	refpt>=25, refcr>180, <300
497		27		54	not required	survived	refpt>=25, refcr>180, <300
498	1675	64	74		not required	survived	refpt>=25, refcr>180, <300
499	4288	60.4		60.4	not required	survived	refpt>=25, refcr<=120
500	4327	99	99	130	dialysis required	Died	refpt>=25, refcr>180, <300
501	7674	73.8	159		dialysis required	Died	refpt>=25, refCr>120, <=180

Number	RIE ALT	RIE PT	High PT inn	High PT man	Dialysis	Survival	REF 8gr according to PT and Cr
502	1333	52.3			not required	survived	refpt<25, refcr>180, <300
503	18269	130			dialysis required	Died	
504	3777	16	38.3		not required	survived	refpt>=25, refcr<=120
505	2979	17		28	not required	survived	refpt>=25, refcr<=120
506	13493	23	32.8	44	not required	survived	refpt<25, refcr<=120
507	2737	38	45		not required	survived	refpt>=25, refcr>=300
508	5122	21.4		48.8	not required	survived	refpt>=25, refCr>120, <=180
509	9011	51	51		not required	survived	refpt>=25, refcr>180, <300
510	4190	38		114	not required	Died	refpt>=25, refcr<=120
511	10000	29	29		not required	survived	
512	10000	65.4		79	dialysis required	survived	refpt>=25, refCr>120, <=180
513	7222	35	68	35	not required	survived	refpt>=25, refcr<=120
514	10000	29	38.6		not required	survived	refpt<25, refcr<=120
515	5399	19.9		73	not required	survived	refpt>=25, refcr<=120
516	9960	34.8	59.1		dialysis required	survived	refpt>=25, refcr<=120
517	6529	65		134	not required	survived	refpt<25, refcr>120, <=180
518	4768	30	31		not required	survived	refpt<25, refcr<=120
519	4532	78.6		79	not required	survived	refpt>=25, refcr<=120
520	8718	35	45	50	not required	survived	refpt>=25, refcr<=120
521	4949	35	50	100	not required	survived	
522	10280	75			not required	survived	refpt<25, refcr<=120

Number	gr according to RIE Cr	Delay to Referring hospital	Delay to ref hospital groups	Delay to RIE	Delay to RIE group
1	Cr<=120	72	>48h	84	>48h
2	Cr<=120		Stag OD		stag OD
3	Cr<=120	24	>12<=24		
4	Cr<=120	24	>12<=24	31	>24, <=48h
5	Cr>120, <=180	36	>24<=48		
6	Cr<=120	11	<=12	64	>48h
7	Cr>120, <=180		Stag OD		stag OD
8	Cr>=300	96	>48h	101	>48h
9	Cr<=120	10	<=12	36	>24, <=48h
10	cr>180, <300	52	>48h	59	>48h
11	cr>180, <300	6	<=12	88	>48h
12	cr>180, <300	9	<=12	57	>48h
13	Cr<=120	7	<=12	241	>48h
14	Cr>=300	10	<=12	48	>24, <=48h
15	Cr<=120	20	>12<=24		
16	Cr>120, <=180	24	>12<=24	70	>48h
17	Cr>=300	52	>48h	52	>48h
18	cr>180, <300		Stag OD		stag OD
19	cr>180, <300		Stag OD		stag OD
20					
21	cr>180, <300		Stag OD		stag OD
22	cr>180, <300	36	>24<=48	40	>24, <=48h
23	Cr>=300	33	>24<=48	48	>24, <=48h
24	Cr<=120		Stag OD		stag OD

Number	gr according to RIE Cr	Delay to Referring hospital	Delay to ref hospital groups	Delay to RIE	Delay to RIE group
25	Cr>=300				
26	cr>180, <300	19	>12<=24	65	>48h
27	Cr<=120	56	>48h	66	>48h
28	Cr<=120	32	>24<=48	42	>24, <=48h
29	cr>180, <300		Stag OD		stag OD
30	Cr>=300				
31	Cr<=120	48	>24<=48	60	>48h
32	Cr<=120	18	>12<=24	55	>48h
33	Cr<=120	18	>12<=24	33	>24, <=48h
34	Cr>=300		Stag OD		stag OD
35	cr>180, <300		Stag OD		stag OD
36	Cr<=120		Stag OD	79	>48h
37	cr>180, <300	37	>24<=48	62	>48h
38	Cr<=120	18	>12<=24	68	>48h
39	Cr>=300	48	>24<=48	53	>48h
40	Cr>=300	42	>24<=48	110	>48h
41	cr>180, <300	96	>48h		
42	Cr>=300				
43	Cr>=300	9	<=12	71	>48h
44	Cr<=120	12	<=12	75	>48h
45	Cr<=120	24	>12<=24	53	>48h
46	Cr<=120	5	<=12	53	>48h
47	Cr<=120	36	>24<=48	78	>48h
48	Cr>=300		Stag OD		stag OD
49	Cr<=120		Stag OD		stag OD
50	Cr>=300		Stag OD		stag OD
51	Cr>120, <=180	4	<=12	48	>24, <=48h
52	Cr>=300	6	<=12	40	>24, <=48h
53	Cr<=120	26	>24<=48	55	>48h
54	Cr<=120	20	>12<=24	51	>48h
55	Cr<=120				
56	Cr<=120	48	>24<=48	72	
57	cr>180, <300		Stag OD	26	>24, <=48h
58	Cr<=120	51	>48h	69	>48h
59	Cr<=120	61	>48h	65	>48h
60	Cr<=120	8	<=12		
61	Cr<=120	19	>12<=24		
62	Cr<=120	23	>12<=24		
63	cr>180, <300	23	>12<=24	77	>48h
64	Cr<=120	16	>12<=24	38	>24, <=48h
65	Cr<=120	9	<=12	20	>12, <=24h
66	cr>180, <300	18	>12<=24	29	>24, <=48h
67	Cr>120, <=180	1	<=12	52	>48h
68			Stag OD		stag OD
69	Cr>120, <=180	8	<=12	54	>48h
70	Cr<=120	16	>12<=24	68	>48h
71	Cr<=120		Stag OD		stag OD
72	Cr<=120	17	>12<=24	25	>24, <=48h
73	Cr>=300	28	>24<=48	54	>48h
74	Cr<=120	45	>24<=48	64	>48h
75	Cr<=120	15	>12<=24	60	>48h
76	cr>180, <300	18	>12<=24	59	>48h

Number	gr according to RIE Cr	Delay to Referring hospital	Delay to ref hospital groups	Delay to RIE	Delay to RIE group
77	Cr<=120	11	<=12	46	>24, <=48h
78	cr>180, <300	59	>48h	72	
79	Cr<=120	27	>24<=48	55	>48h
80	Cr<=120				
81	Cr>120, <=180	42	>24<=48	75	>48h
82	Cr<=120	19	>12<=24	70	>48h
83	Cr<=120	36	>24<=48	47	>24, <=48h
84	Cr<=120	26	>24<=48	50	>48h
85	Cr<=120	18	>12<=24	40	>24, <=48h
86	Cr<=120		Stag OD		stag OD
87	Cr>120, <=180	22	>12<=24	46	>24, <=48h
88	Cr<=120	22	>12<=24	88	>48h
89	Cr>120, <=180	12	<=12	60	>48h
90	Cr>180, <300	72	>48h	96	>48h
91	Cr<=120	27	>24<=48	52	>48h
92	Cr<=120		Stag OD		stag OD
93	Cr>=300	71	>48h	75	>48h
94	Cr<=120	18	>12<=24	45	>24, <=48h
95	Cr>120, <=180	10	<=12	47	>24, <=48h
96	Cr>120, <=180				
97	Cr>=300		Stag OD		stag OD
98	Cr>120, <=180	16	>12<=24	70	>48h
99	Cr>120, <=180	44	>24<=48	48	>24, <=48h
100	Cr<=120		Stag OD		stag OD
101	Cr>=300	48	>24<=48	54	>48h
102	Cr>120, <=180	16	>12<=24	65	>48h
103	Cr>120, <=180	12	<=12	74	>48h
104	cr>180, <300				
105	Cr<=120		Stag OD		stag OD
106	Cr>=300	72	>48h	80	>48h
107	cr>180, <300	36	>24<=48	36	>24, <=48h
108	Cr<=120		Stag OD		stag OD
109	Cr<=120		Stag OD		stag OD
110	Cr>=300		Stag OD		stag OD
111	Cr<=120	17	>12<=24	36	>24, <=48h
112	cr>180, <300				
113	Cr<=120	27	>24<=48	36	>24, <=48h
114					
115	cr>180, <300	22	>12<=24	38	>24, <=48h
116	Cr<=120				
117	Cr<=120	13	>12<=24	45	>24, <=48h
118	cr>180, <300	44	>24<=48	66	>48h
119	Cr>120, <=180	13	>12<=24	34	>24, <=48h
120	Cr<=120	14	>12<=24	67	>48h
121	Cr>120, <=180	44	>24<=48	61	>48h
122	Cr>=300		Stag OD		stag OD
123	Cr<=120	5	<=12	20	>12, <=24h
124	Cr>=300		Stag OD		stag OD
125	Cr>=300		Stag OD		stag OD
126	Cr<=120	28	>24<=48	60	>48h
127	Cr>120, <=180		Stag OD		stag OD
128	Cr>120, <=180	45	>24<=48	50	>48h

Number	gr according to RIE Cr	Delay to Referring hospital	Delay to ref hospital groups	Delay to RIE	Delay to RIE group
129	Cr>120, <=180				
130	Cr<=120				
131	cr>180, <300		Stag OD		stag OD
132	Cr>120, <=180	20	>12<=24	75	>48h
133	Cr<=120	3	<=12	65	>48h
134	cr>180, <300	36	>24<=48	60	>48h
135	Cr>=300		Stag OD		stag OD
136	Cr>120, <=180		Stag OD		stag OD
137	Cr<=120				
138	Cr<=120	3	<=12	64	>48h
139	Cr>120, <=180		Stag OD		stag OD
140	Cr<=120	23	>12<=24	69	>48h
141	cr>180, <300	47	>24<=48	50	>48h
142	Cr<=120		Stag OD	36	>24, <=48h
143	Cr>=300	26	>24<=48	50	>48h
144	Cr<=120	24	>12<=24	30	>24, <=48h
145	Cr<=120	16	>12<=24		
146	cr>180, <300				
147	Cr>=300		Stag OD	72	stag OD
148	Cr<=120	41	>24<=48	64	>48h
149	Cr>120, <=180		Stag OD	48	>24, <=48h
150	Cr<=120	16	>12<=24	53	>48h
151	cr>180, <300		Stag OD		stag OD
152	Cr<=120	12	<=12	21	>12, <=24h
153	Cr<=120	25	>24<=48	52	>48h
154	Cr>120, <=180				
155	Cr>120, <=180	35	>24<=48	40	>24, <=48h
15	Cr>=300				
157		1	<=12		
158	Cr<=120	17	>12<=24	50	>48h
159	Cr<=120	7	<=12	40	>24, <=48h
160	Cr>=300	17	>12<=24	65	>48h
161	cr>180, <300	24	>12<=24	72	
162	Cr<=120	47	>24<=48	56	>48h
163	Cr<=120		Stag OD		stag OD
164	Cr>=300		Stag OD		stag OD
165	Cr<=120	13	>12<=24	21	>12, <=24h
166		30	>24<=48	82	>48h
167	Cr<=120				
168	Cr>120, <=180	16	>12<=24	48	>24, <=48h
169	Cr<=120	5	<=12		
170	cr>180, <300	68	>48h	68	>48h
171	Cr<=120		Stag OD		stag OD
172	Cr<=120	26	>24<=48	44	>24, <=48h
173	Cr<=120		Stag OD		stag OD
174	Cr>120, <=180		Stag OD		stag OD
175	Cr>=300	20	>12<=24		
176	Cr>120, <=180	33	>24<=48	79	>48h
177	Cr<=120	17	>12<=24		
178	Cr<=120		Stag OD		stag OD
179	Cr>120, <=180	36	>24<=48	71	>48h
180	Cr<=120	19	>12<=24	45	>24, <=48h

Number	gr according to RIE Cr	Delay to Referring hospital	Delay to ref hospital groups	Delay to RIE	Delay to RIE group
181	cr>180, <300				
182	Cr>=300	77	>48h	86	>48h
183	Cr<=120	28	>24<=48	41	>24, <=48h
184	cr>180, <300				
185	Cr>=300				
186	Cr>120, <=180	57	>48h	61	>48h
187	cr>180, <300	8	<=12	51	>48h
188	Cr>120, <=180		Stag OD		stag OD
189	Cr<=120	60	>48h	70	>48h
190	Cr<=120		Stag OD		stag OD
191	cr>180, <300	36	>24<=48	48	>24, <=48h
192	Cr>=300		Stag OD		stag OD
193	Cr<=120	14	>12<=24	28	>24, <=48h
194	cr>180, <300		Stag OD		stag OD
195	Cr<=120	45	>24<=48	50	>48h
196		20	>12<=24	64	>48h
197	Cr<=120	22	>12<=24	44	>24, <=48h
198	Cr<=120		Stag OD		stag OD
199	cr>180, <300	18	>12<=24	39	>24, <=48h
200	Cr>=300	26	>24<=48	36	>24, <=48h
201	cr>180, <300		Stag OD		stag OD
202	Cr<=120	31	>24<=48	37	>24, <=48h
203	cr>180, <300	36	>24<=48	46	>24, <=48h
204	Cr>=300	48	>24<=48	54	>48h
205	Cr<=120			70	>48h
206	Cr<=120	36	>24<=48	50	>48h
207	cr>180, <300	7	<=12	71	>48h
208	Cr<=120	14	>12<=24	48	>24, <=48h
209	cr>180, <300	33	>24<=48	51	>48h
210	cr>180, <300	8	<=12	48	>24, <=48h
211	Cr<=120	24	>12<=24	54	>48h
212	cr>180, <300				
213	Cr>120, <=180		Stag OD		stag OD
214	Cr>120, <=180	22	>12<=24	25	>24, <=48h
215	cr>180, <300	31	>24<=48	54	>48h
216	Cr>120, <=180		Stag OD		stag OD
217	cr>180, <300	19	>12<=24	49	>48h
218	Cr>120, <=180	23	>12<=24	29	>24, <=48h
219	Cr<=120	57	>48h	63	>48h
220	Cr>120, <=180	45	>24<=48	52	>48h
221	Cr<=120	52	>48h	60	>48h
222	cr>180, <300		Stag OD		stag OD
223	cr>180, <300	42	>24<=48	51	>48h
224			Stag OD		stag OD
225	cr>180, <300		Stag OD		stag OD
226	cr>180, <300		Stag OD		stag OD
227	Cr<=120				
228	Cr>120, <=180	41	>24<=48	58	>48h
229	Cr<=120	15	>12<=24	91	>48h
230	Cr>=300				
231	Cr>=300				
232	Cr>=300		Stag OD		stag OD

Number	gr according to RIE Cr	Delay to Referring hospital	Delay to ref hospital groups	Delay to RIE	Delay to RIE group
233	Cr<=120	32	>24<=48	39	>24, <=48h
234	Cr<=120	8	<=12	80	>48h
235	Cr>120, <=180	28	>24<=48	12	<=12h
236	Cr<=120	47	>24<=48	55	>48h
237	Cr>120, <=180		Stag OD		stag OD
238	cr>180, <300				
239	Cr<=120	18	>12<=24	65	>48h
240	Cr>=300	48	>24<=48	120	>48h
241	Cr>120, <=180	25	>24<=48	31	>24, <=48h
242	Cr<=120	21	>12<=24	27	>24, <=48h
243	Cr>=300	50	>48h	66	>48h
244	Cr<=120	91	>48h	101	>48h
245	Cr<=120		Stag OD		stag OD
246	Cr<=120	48	>24<=48		
247	cr>180, <300				
248	Cr>=300		Stag OD		stag OD
249	Cr>120, <=180				
250	cr>180, <300	36	>24<=48	51	>48h
251	Cr<=120	8	<=12	80	>48h
252	Cr<=120	41	>24<=48	46	>24, <=48h
253	cr>180, <300				
254	Cr>120, <=180	12	<=12	96	>48h
255	cr>180, <300				
256	Cr>120, <=180	20	>12<=24		
257	Cr>=300	14	>12<=24	84	>48h
258	Cr>=300	50	>48h	98	>48h
259	Cr>120, <=180				
260	Cr<=120	14	>12<=24	62	>48h
261	cr>180, <300	14	>12<=24	72	
262	Cr<=120				
263	cr>180, <300				
264	Cr<=120	12	<=12		
265	Cr>120, <=180				
266	Cr<=120	26	>24<=48	42	>24, <=48h
267	cr>180, <300		Stag OD		stag OD
268	cr>180, <300				
269	Cr<=120	24	>12<=24		
270	Cr<=120		Stag OD		stag OD
271	Cr>=300		Stag OD		stag OD
272	Cr>=300	120	>48h	126	>48h
273	Cr<=120	15	>12<=24	23	>12, <=24h
274	Cr>=300		Stag OD		stag OD
275	Cr<=120				
276	cr>180, <300	24	>12<=24	56	>48h
277	cr>180, <300	24	>12<=24		
278	Cr>=300		Stag OD		stag OD
279	Cr<=120		Stag OD		stag OD
280	Cr>=300		Stag OD		stag OD
281	Cr<=120				
282	Cr<=120	6	<=12	72	
283	Cr>=300				
284	Cr<=120	5	<=12		

Number	gr according to RIE Cr	Delay to Referring hospital	Delay to ref hospital groups	Delay to RIE	Delay to RIE group
285	cr>180, <300		Stag OD		stag OD
286	Cr<=120			50	>48h
287	cr>180, <300				
288	Cr<=120				
289	Cr<=120				
290	Cr<=120	46	>24<=48	58	>48h
291	Cr<=120	7	<=12	30	>24, <=48h
292	Cr>120, <=180		Stag OD		stag OD
293	Cr>=300		Stag OD		stag OD
294	cr>180, <300		Stag OD		stag OD
295	Cr>120, <=180				
296	Cr>=300		Stag OD	7	<=12h
297	cr>180, <300	60	>48h	67	>48h
298	Cr>120, <=180	18	>12<=24	24	>12, <=24h
299	Cr<=120	48	>24<=48	64	>48h
300	Cr<=120	14	>12<=24	42	>24, <=48h
301	Cr<=120				
302	Cr<=120	24	>12<=24	35	>24, <=48h
303	cr>180, <300				
304	Cr>120, <=180			45	>24, <=48h
305					
306	cr>180, <300	88	>48h	92	>48h
307	Cr<=120	18	>12<=24	68	>48h
308	Cr<=120	56	>48h	72	
309	cr>180, <300	48	>24<=48	86	>48h
310	Cr>120, <=180		Stag OD		stag OD
311	Cr<=120	5	<=12	68	>48h
312	Cr>120, <=180	25	>24<=48	62	>48h
313	Cr<=120	40	>24<=48	47	>24, <=48h
314	Cr<=120	6	<=12	72	
315	Cr<=120	40	>24<=48	93	>48h
316	cr>180, <300	26	>24<=48	36	>24, <=48h
317	Cr>120, <=180	3	<=12	83	>48h
318	Cr<=120	15	>12<=24	38	>24, <=48h
319	Cr>120, <=180	48	>24<=48	80	>48h
320	Cr>=300				
321	cr>180, <300	48	>24<=48	58	>48h
322	Cr>=300		Stag OD	40	>24, <=48h
323	Cr<=120		Stag OD		stag OD
324	cr>180, <300				
325	Cr<=120	48	>24<=48	50	>48h
326	Cr>120, <=180		Stag OD		stag OD
327					
328	Cr<=120	48	>24<=48	60	>48h
329	cr>180, <300				
330					
331	Cr<=120	29	>24<=48	66	>48h
332	Cr<=120	12	<=12		
333	Cr>=300	24	>12<=24	50	>48h
334	Cr<=120	40	>24<=48	48	>24, <=48h
335	Cr<=120	51	>48h	57	>48h
336	Cr<=120	10	<=12	63	>48h

Number	gr according to RIE Cr	Delay to Referring hospital	Delay to ref hospital groups	Delay to RIE	Delay to RIE group
337	Cr>=300	11	<=12	44	>24, <=48h
338	Cr<=120	19	>12<=24	54	>48h
339	Cr<=120	24	>12<=24	48	>24, <=48h
340	Cr>120, <=180				
341	Cr<=120	20	>12<=24	52	>48h
342	Cr<=120	12	<=12		
343	cr>180, <300	43	>24<=48	60	>48h
344	Cr<=120		Stag OD		stag OD
345	Cr<=120				
346	cr>180, <300	44	>24<=48	57	>48h
347	Cr<=120	16	>12<=24	72	
348	cr>180, <300	52	>48h	59	>48h
349	cr>180, <300				
350	Cr>=300		Stag OD		stag OD
351	cr>180, <300	8	<=12		
352	Cr<=120	16	>12<=24	48	>24, <=48h
353	Cr<=120		Stag OD		stag OD
354		19	>12<=24	39	>24, <=48h
355	Cr>120, <=180	36	>24<=48	64	>48h
356	Cr<=120	18	>12<=24	50	>48h
357	cr>180, <300	56	>48h	67	>48h
358	Cr>120, <=180		Stag OD		stag OD
359	Cr<=120	68	>48h	72	
360	Cr<=120	22	>12<=24	42	>24, <=48h
361	Cr<=120		Stag OD		stag OD
362	Cr<=120	55	>48h	62	>48h
363	Cr>=300	72	>48h		
364	Cr<=120	19	>12<=24	37	>24, <=48h
365	Cr>=300		Stag OD		stag OD
366	cr>180, <300	57	>48h	68	>48h
367	Cr<=120	11	<=12	38	>24, <=48h
368	Cr>120, <=180		Stag OD		stag OD
369	Cr>=300	45	>24<=48	54	>48h
370	Cr>120, <=180		Stag OD		stag OD
371	Cr>=300		Stag OD		stag OD
372	Cr>120, <=180		Stag OD		stag OD
373	Cr>=300		Stag OD		stag OD
374	Cr>120, <=180		Stag OD		stag OD
375	Cr<=120	7	<=12	60	>48h
376	Cr<=120	15	>12<=24	21	>12, <=24h
377	Cr>=300		Stag OD		stag OD
378	Cr<=120	17	>12<=24	29	>24, <=48h
379	cr>180, <300	16	>12<=24		
380	Cr>=300		Stag OD		stag OD
381	Cr<=120	14	>12<=24	48	>24, <=48h
382	Cr>=300		Stag OD		stag OD
383	cr>180, <300	48	>24<=48		
384	cr>180, <300		Stag OD		stag OD
385	cr>180, <300	16	>12<=24	69	>48h
386	cr>180, <300	66	>48h	74	>48h
387	Cr<=120	15	>12<=24	70	>48h
388	cr>180, <300	29	>24<=48	41	>24, <=48h

Number	gr according to RIE Cr	Delay to Referring hospital	Delay to ref hospital groups	Delay to RIE	Delay to RIE group
389	Cr>120, <=180	15	>12<=24	60	>48h
390	Cr<=120				
391	Cr>=300	130	>48h	130	>48h
392	Cr>=300	55	>48h	72	
393	Cr<=120	12	<=12	67	>48h
394	Cr<=120	1	<=12	78	>48h
395	cr>180, <300	11	<=12	24	>12, <=24h
396	Cr>120, <=180	22	>12<=24	52	>48h
397	cr>180, <300	54	>48h	60	>48h
398	Cr<=120		Stag OD		stag OD
399	Cr<=120		Stag OD		stag OD
400	Cr<=120		Stag OD		stag OD
401	Cr>120, <=180	24	>12<=24	30	>24, <=48h
402	Cr<=120				
403	Cr<=120	19	>12<=24	89	>48h
404	cr>180, <300		Stag OD		stag OD
405	Cr>=300				
406	Cr>=300	48	>24<=48	72	
407	Cr<=120	18	>12<=24		
408	Cr<=120	22	>12<=24	36	>24, <=48h
409	Cr>120, <=180		Stag OD		stag OD
410	Cr<=120	23	>12<=24	69	>48h
411	Cr>=300	48	>24<=48		
412	Cr<=120	27	>24<=48	74	>48h
413	Cr<=120	24	>12<=24	64	>48h
414	Cr>=300		Stag OD		stag OD
415	Cr>=300		Stag OD		stag OD
416	Cr<=120	22	>12<=24	72	
417	Cr>120, <=180	72	>48h	86	>48h
418	Cr>=300		Stag OD		stag OD
419	cr>180, <300		Stag OD	50	>48h
420	Cr<=120	27	>24<=48	42	>24, <=48h
421	cr>180, <300	28	>24<=48	39	>24, <=48h
422	Cr>=300		Stag OD		stag OD
423	Cr<=120	30	>24<=48	46	>24, <=48h
424	Cr<=120		Stag OD		stag OD
425	Cr>120, <=180	12	<=12	44	>24, <=48h
526	Cr<=120		Stag OD		stag OD
427	Cr<=120	16	>12<=24	1	<=12h
428	Cr<=120	86	>48h	86	>48h
429	Cr>120, <=180	40	>24<=48	62	>48h
430	cr>180, <300		Stag OD		stag OD
431	Cr>=300				
432	Cr<=120	5	<=12	67	>48h
433	Cr<=120	24	>12<=24		
434	Cr>120, <=180				
435	Cr<=120	6	Stag OD	56	>48h
436	Cr<=120	46	>24<=48	48	>24, <=48h
437	Cr>120, <=180		Stag OD	55	>48h
438	cr>180, <300	30	>24<=48	36	>24, <=48h
439	Cr<=120	34	>24<=48	72	
440	Cr>120, <=180	16	>12<=24	36	>24, <=48h

Number	gr according to RIE Cr	Delay to Referring hospital	Delay to ref hospital groups	Delay to RIE	Delay to RIE group
441	Cr<=120	20	>12<=24	51	>48h
442	Cr>=300		Stag OD		stag OD
443	Cr<=120		Stag OD		stag OD
444	Cr<=120	12	<=12		
445	Cr<=120	18	>12<=24	66	>48h
446	Cr>120, <=180				
447	Cr>=300		Stag OD		stag OD
448	cr>180, <300				
449	Cr<=120		Stag OD	22	>12, <=24h
450	Cr<=120		Stag OD		stag OD
451	Cr<=120		Stag OD		stag OD
452	Cr>=300		Stag OD		stag OD
453	Cr<=120	15	>12<=24		
454	cr>180, <300	18	>12<=24	74	>48h
455	cr>180, <300	26	>24<=48		
456	Cr>=300				
457	Cr<=120	48	>24<=48	72	
458	Cr<=120	48	>24<=48	48	>24, <=48h
459	Cr<=120	28	>24<=48	57	>48h
460	cr>180, <300		Stag OD		stag OD
461	Cr<=120	36	>24<=48		
462	Cr<=120	6	<=12		
463	Cr<=120				
464	Cr>=300				
465	Cr<=120	36	>24<=48	72	
466	Cr<=120	10	<=12	45	>24, <=48h
467	Cr>120, <=180	43	>24<=48		
468	Cr<=120	58	>48h		
469	Cr<=120		Stag OD		stag OD
470	Cr>120, <=180	32	>24<=48	35	>24, <=48h
471	Cr>120, <=180	26	>24<=48	37	>24, <=48h
472	Cr<=120		Stag OD	35	>24, <=48h
473	Cr<=120	17	>12<=24	24	>12, <=24h
474	cr>180, <300	56	>48h	100	>48h
475	Cr<=120		Stag OD		stag OD
476	cr>180, <300	48	>24<=48		
477	Cr>=300	11	<=12	59	>48h
478	Cr<=120	14	>12<=24		
479	Cr<=120	11	<=12	57	>48h
480	cr>180, <300				
481	Cr<=120		Stag OD		stag OD
482	Cr<=120	5	<=12	48	>24, <=48h
483	cr>180, <300				
484	Cr<=120	21	>12<=24	46	>24, <=48h
485	Cr>=300	24	>12<=24	55	>48h
486	Cr<=120	22	>12<=24		
487	Cr<=120	16	>12<=24	42	>24, <=48h
488	Cr<=120		Stag OD		stag OD
489	Cr<=120	17	>12<=24	54	>48h
490	Cr>120, <=180	16	>12<=24	46	>24, <=48h
491	Cr>120, <=180	20	>12<=24	52	>48h
492	Cr<=120	18	>12<=24	42	>24, <=48h

Number	gr according to RIE Cr	Delay to Referring hospital	Delay to ref hospital groups	Delay to RIE	Delay to RIE group
493	Cr<=120	62	>48h	68	>48h
494	Cr<=120	31	>24<=48	54	>48h
495	cr>180, <300	23	>12<=24		
496	Cr>120, <=180	7	<=12	72	
497	cr>180, <300		Stag OD		stag OD
498	cr>180, <300		Stag OD	96	>48h
499	Cr<=120		Stag OD		stag OD
500	cr>180, <300	36	>24<=48	42	>24, <=48h
501	Cr>120, <=180	33	>24<=48	41	>24, <=48h
502	Cr>120, <=180	52	>48h	108	>48h
503	Cr>=300		Stag OD		stag OD
504	cr>180, <300		Stag OD		stag OD
505	Cr<=120				
506	cr>180, <300		Stag OD		stag OD
507	Cr>120, <=180		Stag OD		stag OD
508	Cr<=120				
509	cr>180, <300	32	>24<=48	62	>48h
510	Cr<=120	18	>12<=24	22	>12, <=24h
511	Cr<=120		Stag OD		stag OD
512	Cr>120, <=180	40	>24<=48	48	>24, <=48h
513	Cr<=120		Stag OD		stag OD
514	Cr<=120	21	>12<=24	47	>24, <=48h
515	Cr<=120	12	<=12	48	>24, <=48h
516	cr>180, <300	37	>24<=48	72	
517	Cr<=120				
518	Cr<=120	24	>12<=24	50	>48h
519	Cr>120, <=180		Stag OD		stag OD
520	Cr<=120			67	>48h
521	Cr<=120	17	>12<=24	44	>24, <=48h
522	Cr<=120	18	>12<=24	40	>24, <=48h

Number	Outcome	ITU Stay	RIE Stay	SLTU Stay
1	SURVIVED NO TP	0	3	3
2	SURVIVED NO TP	0	6	6
3	DIED NO TP	2	2	0
4	DIED NO TP	5	6	1
5	DIED NO TP	1	1	0
6	SURVIVED NO TP	0	4	4
7	DIED NO TP	3	5	2
8	DIED NO TP	1	1	0
9	SURVIVED NO TP	0	6	5
10	SURVIVED NO TP	0	8	8
11	SURVIVED NO TP	0	2	2
12	SURVIVED NO TP	0	3	9
13	DIED WITH TP	19	21	2
14	SURVIVED NO TP	0	9	9
15	SURVIVED NO TP	0	7	7

Number	Outcome	ITU Stay	RIE Stay	SLTU Stay
16	SURVIVED NO TP	0	5	5
17	SURVIVED WITH TP	5	98	93
18	SURVIVED NO TP	0	9	9
19	DIED NO TP	4	5	2
20	DIED NO TP	3	3	0
21	DIED NO TP	24	24	0
22	SURVIVED WITH TP	31	69	38
23	DIED NO TP	2	3	1
24	SURVIVED NO TP	0	5	5
25	DIED NO TP	8	9	1
26	SURVIVED NO TP	3	9	6
27	SURVIVED NO TP	0	3	3
28	SURVIVED NO TP	0	4	4
29	SURVIVED NO TP	0	6	6
30	SURVIVED NO TP	5	9	4
31	SURVIVED NO TP	0	6	6
32	SURVIVED NO TP	0	4	4
33	SURVIVED NO TP	0	11	0
34	DIED NO TP	11	11	0
35	DIED NO TP	10	10	1
36	SURVIVED NO TP	0	3	3
37	SURVIVED NO TP	0	7	7
38	SURVIVED NO TP	0	3	3
39	SURVIVED NO TP	0	47	47
40	SURVIVED NO TP	10	15	6
41	SURVIVED WITH TP	1	112	111
42	DIED NO TP	1	1	0
43	SURVIVED NO TP	0	13	13
44	SURVIVED NO TP	0	6	6
45	SURVIVED NO TP	0	4	4
46	SURVIVED NO TP	0	4	4
47	SURVIVED NO TP	0	4	4
48	DIED NO TP	6	6	0
49	DIED NO TP	11	13	3
50	DIED NO TP	5	7	0
51	DIED NO TP	10	10	0
52	DIED NO TP	2	2	0
53	SURVIVED NO TP	0	5	5
54	SURVIVED NO TP	0	7	7
55	SURVIVED NO TP	0	3	3
56	SURVIVED NO TP	0	7	7
57	SURVIVED NO TP	0	9	9
58	SURVIVED NO TP			
59	SURVIVED NO TP	10	11	2
60	SURVIVED NO TP	0	6	6
61	SURVIVED NO TP	2	7	5
62	SURVIVED NO TP	0	4	4
63	SURVIVED NO TP	0	18	16
64	DIED WITH TP	8	12	7
65	SURVIVED NO TP	0	5	5
66	DIED WITH TP	3	36	33
67	SURVIVED NO TP	0	6	6
68	DIED NO TP		3	.

Number	Outcome	ITU Stay	RIE Stay	SLTU Stay
69	SURVIVED NO TP	0	4	4
70	SURVIVED NO TP	0	4	4
71	SURVIVED NO TP	0	3	3
72	SURVIVED NO TP	0	4	4
73	DIED NO TP	5	8	4
74	SURVIVED NO TP	0	5	5
75	SURVIVED NO TP	0	4	4
76	SURVIVED NO TP	0	6	6
77	SURVIVED NO TP	0	4	4
78	SURVIVED NO TP	4	13	9
79	SURVIVED NO TP	0	4	4
80	SURVIVED NO TP	0	4	4
81	DIED WITH TP	18	19	1
82	SURVIVED NO TP	0	7	7
83	SURVIVED NO TP	0	4	4
84	SURVIVED NO TP	0	3	3
85	SURVIVED NO TP	0	6	6
86	SURVIVED NO TP	0	3	3
87	SURVIVED NO TP	0	3	3
88	SURVIVED NO TP	0	5	5
89	SURVIVED NO TP	0	5	5
90	SURVIVED NO TP	5	5	0
91	SURVIVED NO TP	0	9	9
92	SURVIVED NO TP	0	6	6
93	DIED NO TP	3	4	1
94	SURVIVED NO TP	0	5	5
95	SURVIVED NO TP	0	14	14
96	DIED NO TP	2	2	1
97	DIED NO TP	9	10	2
98	SURVIVED NO TP	5	9	6
99	SURVIVED NO TP	0	10	10
100	SURVIVED NO TP	5	19	14
101	DIED NO TP	1	2	1
102	SURVIVED NO TP	0	3	3
103	SURVIVED NO TP	0	23	23
104	DIED NO TP	7	7	0
105	SURVIVED NO TP	0	4	4
106	DIED NO TP	2	2	0
107	DIED NO TP	0	2	2
108	SURVIVED NO TP	0	3	3
109	SURVIVED NO TP	0	5	5
110	SURVIVED NO TP	2	11	13
111	SURVIVED NO TP	2	10	11
112	DIED NO TP	1	1	1
113	DIED NO TP	5	6	2
114	DIED NO TP	2	4	2
115	DIED NO TP	5	7	3
116	SURVIVED NO TP	0	3	3
117	SURVIVED NO TP	0	7	7
118	DIED NO TP	11	11	0
119	DIED NO TP	15	18	4
120	SURVIVED NO TP	0	3	3
121	SURVIVED NO TP	0	9	9

Number	Outcome	ITU Stay	RIE Stay	SLTU Stay
122	SURVIVED NO TP	0	4	4
123	DIED NO TP	6	7	1
124	DIED NO TP	1	1	0
125	SURVIVED NO TP	0	8	8
126	SURVIVED NO TP	0	4	4
127	DIED NO TP	3	4	2
128	SURVIVED NO TP	0	4	4
129	SURVIVED WITH TP	7	27	20
130	SURVIVED NO TP	4	11	7
131	DIED NO TP	3	3	1
132	SURVIVED NO TP	0	5	5
133	SURVIVED NO TP	0	6	4
134	DIED NO TP	12	14	1
135	DIED NO TP	2	2	0
136	SURVIVED NO TP	0	13	13
137	DIED NO TP	0	3	2
138	SURVIVED NO TP	0	4	4
139	SURVIVED NO TP	0	10	10
140	SURVIVED NO TP	0	5	5
141	SURVIVED NO TP	0	13	13
142	SURVIVED NO TP	0	5	5
143	DIED NO TP	0	3	2
144	SURVIVED NO TP	0	8	8
145	SURVIVED NO TP	0	5	5
146	DIED NO TP	2	2	0
147	DIED NO TP	2	2	0
148	SURVIVED NO TP	0	6	6
149	SURVIVED NO TP	4	13	7
150	SURVIVED NO TP	0	14	14
151	SURVIVED NO TP	0	6	6
152	SURVIVED NO TP	0	3	3
153	SURVIVED NO TP	0	6	6
154	DIED NO TP	0	2	2
155	DIED NO TP	5	6	2
15	DIED NO TP	2	2	0
157	SURVIVED NO TP	8	15	7
158	SURVIVED NO TP	0	3	3
159	SURVIVED NO TP	10	24	14
160	DIED NO TP	4	5	1
161	SURVIVED NO TP	9	19	10
162	SURVIVED NO TP	0	6	6
163	SURVIVED NO TP	6	11	4
164	SURVIVED NO TP	3	5	3
165	SURVIVED NO TP	7	10	3
166	SURVIVED NO TP	1	8	7
167	SURVIVED NO TP	0	4	4
168	SURVIVED NO TP		8	.
169	SURVIVED NO TP	8	14	6
170	SURVIVED WITH TP	6	25	19
171	SURVIVED NO TP	0	4	4
172	SURVIVED NO TP	0	5	5
173	SURVIVED NO TP	0	10	10
174	SURVIVED NO TP	0	5	5

Number	Outcome	ITU Stay	RIE Stay	SLTU Stay
175	SURVIVED WITH TP	7	24	17
176	DIED WITH TP	5	5	0
177	SURVIVED NO TP	0	4	4
178	SURVIVED NO TP	0	10	10
179	SURVIVED NO TP	0	6	6
180	SURVIVED NO TP	0	5	5
181	DIED NO TP	4	4	0
182	SURVIVED NO TP	0	5	5
183	SURVIVED NO TP	0	8	8
184	DIED NO TP	2	2	0
185	SURVIVED NO TP	21	25	8
186	SURVIVED NO TP	0	4	4
187	SURVIVED WITH TP	7	33	26
188	DIED NO TP	3	3	1
189	SURVIVED NO TP	0	3	3
190	SURVIVED NO TP	0	4	4
191	SURVIVED NO TP	0	8	8
192	DIED NO TP	4	5	2
193	SURVIVED WITH TP	3	34	31
194	DIED NO TP	2	2	0
195	SURVIVED NO TP	9	21	12
196	SURVIVED NO TP	0	3	3
197	SURVIVED NO TP	0	5	5
198	SURVIVED NO TP	0	5	5
199	DIED NO TP	2	2	0
200	DIED NO TP	1	2	1
201	DIED NO TP	2	2	1
202	SURVIVED NO TP	0	6	6
203	DIED NO TP	2	3	1
204	SURVIVED NO TP	0	5	5
205	SURVIVED NO TP	0	3	3
206	SURVIVED NO TP	0	4	4
207	SURVIVED NO TP	0	3	3
208	SURVIVED WITH TP	10	38	28
209	SURVIVED WITH TP	7	26	20
210	SURVIVED WITH TP	89	158	69
211	SURVIVED NO TP	0	5	5
212	SURVIVED NO TP	4	5	2
213	SURVIVED NO TP	0	7	7
214	SURVIVED NO TP	0	10	10
215	SURVIVED WITH TP	5	20	15
216	SURVIVED NO TP	0	8	8
217	SURVIVED NO TP	0	8	8
218	DIED NO TP	2	2	0
219	SURVIVED NO TP	0	4	4
220	DIED NO TP	2	2	0
221	SURVIVED NO TP	0	6	6
222	DIED NO TP	5	6	1
223	DIED NO TP	3	4	2
224	SURVIVED NO TP	0	3	3
225	DIED NO TP	2	3	2
226	DIED NO TP	1	1	0
227	SURVIVED NO TP	0	6	6

Number	Outcome	ITU Stay	RIE Stay	SLTU Stay
228	SURVIVED WITH TP	6	37	31
229	SURVIVED NO TP	0	4	4
230	DIED NO TP	2	2	0
231	DIED NO TP	2	4	0
232	SURVIVED NO TP	13	23	12
233	SURVIVED WITH TP	7	31	26
234	SURVIVED NO TP	10	5	5
235	SURVIVED WITH TP	5	18	14
236	SURVIVED NO TP	0	4	4
237	SURVIVED WITH TP	3	33	31
238	SURVIVED NO TP	0	19	19
239	SURVIVED NO TP	0	5	5
240	SURVIVED NO TP	0	10	2
241	DIED NO TP	0	4	4
242	SURVIVED NO TP	0	4	4
243	SURVIVED NO TP	0	6	6
244	SURVIVED NO TP	0	3	3
245	SURVIVED NO TP	0	5	5
246	SURVIVED WITH TP	15	60	47
247	DIED NO TP	2	2	0
248	SURVIVED NO TP	2	13	12
249	SURVIVED WITH TP	12	28	18
250	SURVIVED WITH TP	33	67	34
251	SURVIVED NO TP	0	3	3
252	SURVIVED NO TP	0	7	7
253	DIED NO TP	0	2	2
254	SURVIVED NO TP	0	4	4
255	DIED WITH TP	3	3	1
256	SURVIVED NO TP	0	3	3
257	SURVIVED NO TP	0	4	4
258	SURVIVED NO TP	2	15	13
259	SURVIVED NO TP	4	15	11
260	SURVIVED NO TP	3	6	3
261	SURVIVED NO TP	0	3	3
262	SURVIVED NO TP	7	14	7
263	SURVIVED NO TP	0	4	4
264	SURVIVED NO TP	0	5	5
265	DIED NO TP	3	3	0
266	SURVIVED NO TP	0	7	7
267	SURVIVED WITH TP	13	25	14
268	DIED NO TP	5	5	1
269	DIED NO TP	0	3	3
270	SURVIVED NO TP	0	3	3
271	DIED NO TP	15	16	1
272	DIED NO TP	2	2	0
273	DIED NO TP	12	13	2
274	DIED NO TP	1	1	0
275	SURVIVED NO TP	0	5	5
276	DIED NO TP	1	1	1
277	SURVIVED WITH TP	10	49	39
278	DIED NO TP	2	2	0
279	SURVIVED NO TP	1	9	8
280	SURVIVED WITH TP	8	19	12

Number	Outcome	ITU Stay	RIE Stay	SLTU Stay
281	SURVIVED NO TP	0	6	6
282	SURVIVED NO TP	0	2	2
283	SURVIVED NO TP	7	16	9
284	SURVIVED NO TP	0	17	17
285	DIED NO TP	2	2	0
286	SURVIVED NO TP	6	10	4
287	DIED NO TP	6	8	2
288	SURVIVED NO TP	0	4	4
289	SURVIVED NO TP	4	11	7
290	SURVIVED NO TP	0	5	5
291	SURVIVED NO TP	0	9	9
292	SURVIVED NO TP	3	22	20
293	SURVIVED NO TP	0	6	6
294	DIED NO TP	1	1	0
295	DIED NO TP	7	8	1
296	SURVIVED NO TP	2	13	10
297	SURVIVED NO TP	0	11	11
298	DIED WITH TP	2	2	0
299	SURVIVED NO TP	0	3	3
300	SURVIVED NO TP	0	3	3
301	SURVIVED NO TP	0	2	2
302	DIED NO TP	2	3	1
303	SURVIVED NO TP	0	7	7
304	SURVIVED NO TP	0	6	6
305	DIED NO TP	2	2	0
306	DIED NO TP	16	19	7
307	SURVIVED NO TP	0	3	3
308	SURVIVED NO TP	0	3	3
309	SURVIVED NO TP	0	6	6
310	SURVIVED NO TP	0	5	5
311	SURVIVED NO TP	0	10	6
312	SURVIVED NO TP	0	15	2
313	SURVIVED NO TP	0	4	4
314	SURVIVED NO TP	0	3	3
315	SURVIVED NO TP	0	4	4
316	SURVIVED NO TP	3	13	11
317	SURVIVED NO TP	0	5	5
318	SURVIVED NO TP	0	6	6
319	DIED NO TP	3	4	1
320	DIED NO TP	20	22	2
321	DIED NO TP	1	1	1
322	DIED NO TP	0	3	3
323	SURVIVED NO TP	3	9	6
324	SURVIVED NO TP			
325	DIED NO TP	2	2	0
326	SURVIVED NO TP	0	8	8
327	DIED NO TP	10	10	1
328	SURVIVED NO TP	6	11	5
329	DIED NO TP	10	11	2
330	DIED NO TP	2	2	0
331	SURVIVED NO TP	0	2	2
332	SURVIVED NO TP	0	6	6
333	SURVIVED NO TP	0	5	5

Number	Outcome	ITU Stay	RIE Stay	SLTU Stay
334	SURVIVED NO TP	4	8	4
335	SURVIVED NO TP	5	10	7
336	SURVIVED NO TP	0	2	2
337	SURVIVED NO TP	0	8	8
338	SURVIVED NO TP	0	13	13
339	SURVIVED NO TP	0	3	3
340	DIED NO TP	1	2	1
341	SURVIVED NO TP	0	4	4
342	DIED NO TP	0	14	14
343	SURVIVED NO TP	0	9	9
344	SURVIVED NO TP	0	8	8
345	DIED NO TP	2	3	1
346	DIED NO TP	8	8	1
347	SURVIVED WITH TP	5	28	22
348	DIED NO TP	15	18	3
349	DIED NO TP	2	2	0
350	DIED NO TP	6	6	0
351	SURVIVED NO TP	0	6	6
352	SURVIVED NO TP	3	14	11
353	SURVIVED NO TP	0	5	5
354	DIED NO TP	1	1	0
355	SURVIVED WITH TP	4	24	20
356	SURVIVED NO TP	0	5	5
357	DIED NO TP			
358	SURVIVED NO TP	3	7	4
359	DIED NO TP	7	7	0
360	SURVIVED NO TP	0	12	12
361	SURVIVED NO TP	0	4	4
362	SURVIVED NO TP	0	3	3
363	DIED NO TP	3	3	0
364	SURVIVED NO TP	2	9	9
365	DIED NO TP	13	14	1
366	SURVIVED NO TP	0	5	5
367	SURVIVED NO TP	0	5	5
368	DIED NO TP	4	4	0
369	SURVIVED NO TP	0	6	5
370	DIED NO TP	13	13	0
371	DIED NO TP	3	5	3
372	SURVIVED NO TP	0	3	3
373	SURVIVED NO TP	0	7	7
374	SURVIVED NO TP	0	5	5
375	SURVIVED NO TP	5	18	13
376	SURVIVED NO TP	0	5	5
377	SURVIVED NO TP	0	6	6
378	SURVIVED NO TP	0	3	3
379	SURVIVED NO TP	0	8	8
380	DIED WITH TP	7	7	0
381	SURVIVED NO TP	0	3	3
382	SURVIVED NO TP	0	11	11
383	SURVIVED NO TP	0	4	4
384	DIED NO TP	2	2	0
385	DIED NO TP	4	4	0
386	SURVIVED NO TP	0	5	5

Number	Outcome	ITU Stay	RIE Stay	SLTU Stay
387	SURVIVED NO TP	0	3	3
388	DIED NO TP	2	2	0
389	SURVIVED NO TP	0	4	4
390	SURVIVED NO TP	0	4	4
391	SURVIVED NO TP	13	21	12
392	SURVIVED NO TP	13	18	5
393	SURVIVED NO TP	0	5	5
394	SURVIVED NO TP	0	4	4
395	SURVIVED NO TP	0	10	8
396	SURVIVED NO TP	0	6	6
397	DIED NO TP	2	2	1
398	SURVIVED NO TP	2	5	4
399	SURVIVED NO TP	0	4	4
400	SURVIVED NO TP	0	3	3
401	SURVIVED NO TP	0	7	7
402	SURVIVED NO TP	5	10	5
403	SURVIVED NO TP		13	.
404	DIED NO TP	2	2	0
405	SURVIVED WITH TP	13	37	24
406	SURVIVED NO TP	0	3	3
407	SURVIVED NO TP	0	4	4
408	DIED NO TP	9	9	1
409	DIED NO TP	0	8	8
410	SURVIVED NO TP	0	5	5
411	DIED WITH TP		25	25
412	SURVIVED NO TP	0	3	3
413	SURVIVED NO TP	0	5	5
414	SURVIVED NO TP	0	7	7
415	DIED NO TP	2	2	0
416	SURVIVED NO TP	0	3	3
417	SURVIVED NO TP	0	4	4
418	SURVIVED NO TP	0	7	7
419	SURVIVED NO TP	12	24	11
420	DIED NO TP	2	2	1
421	SURVIVED WITH TP	7	23	17
422	SURVIVED NO TP	0	6	6
423	SURVIVED NO TP	7	18	11
424	SURVIVED NO TP	0	8	8
425	SURVIVED NO TP	0	7	7
526	SURVIVED NO TP	14	25	12
427	SURVIVED NO TP	0	10	10
428	SURVIVED NO TP	0	3	3
429	SURVIVED NO TP	11	24	13
430	DIED NO TP	1	1	0
431	SURVIVED NO TP	13	21	8
432	SURVIVED NO TP	0	3	3
433	SURVIVED NO TP	0	4	4
434	SURVIVED NO TP	9	15	7
435	SURVIVED NO TP	0	5	3
436	SURVIVED NO TP	0	3	3
437	SURVIVED NO TP	0	2	2
438	DIED NO TP	9	10	2
439	SURVIVED NO TP	0	4	4

Number	Outcome	ITU Stay	RIE Stay	SLTU Stay
440	DIED NO TP	3	1	4
441	SURVIVED NO TP	0	6	6
442	DIED NO TP	8	9	1
443	SURVIVED NO TP	17	26	9
444	SURVIVED NO TP	0	3	3
445	SURVIVED NO TP	0	4	4
446	SURVIVED WITH TP	8	26	28
447	DIED WITH TP			
448	DIED NO TP	2	2	0
449	SURVIVED NO TP	0	7	7
450	SURVIVED NO TP	0	11	11
451	SURVIVED NO TP	0	3	3
452	SURVIVED NO TP	0	9	9
453	SURVIVED NO TP	0	3	3
454	SURVIVED NO TP	0	5	5
455	SURVIVED WITH TP	7	34	28
456	DIED NO TP	10	10	0
457	SURVIVED NO TP	0	3	3
458	SURVIVED NO TP	0	3	3
459	SURVIVED NO TP	0	6	6
460	DIED NO TP	3	3	0
461	SURVIVED NO TP	0	3	3
462	SURVIVED NO TP	0	3	3
463	DIED NO TP	9	10	2
464	DIED NO TP	8	8	0
465	SURVIVED NO TP	0	2	2
466	SURVIVED NO TP	0	5	5
467	DIED NO TP	2	2	0
468	SURVIVED NO TP	0	6	6
469	SURVIVED NO TP	0	5	5
470	DIED NO TP	4	5	1
471	DIED NO TP	2	2	1
472	SURVIVED NO TP	0	12	12
473	DIED NO TP	2	3	1
474	SURVIVED NO TP	0	10	10
475	SURVIVED NO TP	3	5	3
476	SURVIVED NO TP	5	20	15
477	SURVIVED NO TP	7	12	5
478	SURVIVED NO TP	0	3	3
479	SURVIVED NO TP	0	5	5
480	DIED NO TP	3	3	0
481	SURVIVED NO TP	6	37	32
482	SURVIVED NO TP	0	6	6
483	DIED NO TP	1	2	1
484	SURVIVED NO TP	0	6	6
485	DIED WITH TP	6	6	0
486	SURVIVED NO TP	0	3	3
487	SURVIVED NO TP	0	5	0
488	DIED NO TP	7	7	0
489	SURVIVED NO TP	0	3	3
490	SURVIVED NO TP	0	12	10
491	SURVIVED NO TP	0	10	10
492	SURVIVED NO TP	0	3	0

Number	Outcome	ITU Stay	RIE Stay	SLTU Stay
493	SURVIVED NO TP	9	16	7
494	SURVIVED NO TP	0	4	4
495	DIED NO TP	3	3	0
496	SURVIVED NO TP	6	12	7
497	SURVIVED NO TP	0	6	6
498	SURVIVED NO TP	0	11	11
499	SURVIVED NO TP	1	6	5
500	DIED NO TP	2	2	1
501	DIED NO TP	2	3	1
502	SURVIVED NO TP	6	12	6
503	DIED WITH TP	2	2	0
504	SURVIVED NO TP	0	3	3
505	SURVIVED NO TP	0	6	6
506	SURVIVED NO TP	0	4	4
507	SURVIVED NO TP	0	3	3
508	SURVIVED NO TP	0	2	2
509	SURVIVED NO TP	7	14	7
510	DIED WITH TP	1	4	3
511	SURVIVED NO TP	0	6	6
512	SURVIVED NO TP	0	11	11
513	SURVIVED NO TP	0	10	10
514	SURVIVED NO TP	0	6	6
515	SURVIVED NO TP	0	6	4
516	SURVIVED NO TP	4	24	20
517	SURVIVED NO TP	1	6	6
518	SURVIVED NO TP	0	4	4
519	SURVIVED NO TP	0	11	11
520	SURVIVED NO TP	0	3	3
521	SURVIVED NO TP	2	11	10
522	SURVIVED NO TP	0	9	1

Number: number of each patient. Code: code for each patient; DOB: date of birth; Ref: referring; Cr: creatinine (µmol/l); Delay: time between ingestion and admission to referring hospital (h); Stag OD: staggered overdose; Asso ALC: associated alcohol; ALC intake: alcohol intake (unit/week); Na: plasma sodium (mmol/l); K: plasma potassium (mmol/l); Bic: plasma bicarbonate (mmol/l); Bil: bilirubin (µmol/l); ALP: alkaline phosphatase (U/l); GGT: gamma glutamyl transpeptidase (U/l); H^+: $[H^+]$ (mmol/l); ALT: alanine transaminase (U/l); PT: prothrombin time (Sec); APTT: partial prothrombin time; ITU stay: intensive care unit stay (day); ref 8gr: 8 groups according to PT and Cr in the referring hospital; TP: transplant; Blank column: missing data.

Appendix 3.2: Subjects who had degrees of renal dysfunction (referring Cr.120 umol/l), but not significant liver impairment (PT<25 sec) at first admission to referring hospital (n=26). Interval: time between ingestion and admission to referring hospital.

Number	Code	DOB	Sex	Age (y)	Ref Cr (µmol/l)	Ref PT (Sec)	Ref ALT (IU/l)	Delay h
1	JA060023	12-Sep-30	male	66.0	123	14	6805	24
2	MB030076	03-Jan-71	female	23.0	130	19	9756	19
3	RB090081	19-Apr-74	male	26.0	126	21.5	11320	16
4	WC110124	19-Aug-39	female	63.0	170	18	844	Unknown
5	WC080132	29-Oct-72	male	26.0	122	13	16852	16
6	FD110154	30-Nov-58	male	41.0	132	21	760	13
7	MH060269	12-Feb-80	female	17.0	131	18	3583	45
8	SH130692	24-Aug-60	male	43.0	155	15	1563	22
9	KM130694	14-Jan-83	male	21.0	155	14	7941	Staggered
10	JM070397	03-Mar-70	male	28.0	136	23.5	11731	missing data
11	JM120673	16-Oct-58	male	45.0	160	22	7184	Staggered
12	RN090495	04-Dec-67	male	23.0	129	21	6163	16
13	BS020575	04-Mar-72	male	21.0	132	15.6	1463	missing data
14	DS040592	07-Sep-70	male	24.0	134	18	45	6
15	AS080602	30-Mar-68	female	31.0	122	21.7	10000	missing data
16	CT080623	24-Jan-65	female	34.0	124	22	9756	22
17	RW090658	16-Oct-65	male	34.0	123	18	6529	missing data
18	SG100237	04-Feb-82	male	29.0	217	22	12280	33
19	EL030354	13-Jan-33	male	61.0	193	18	8800	missing data
20	VM030440	01-Oct-45	male	49.0	284	23	10910	11
21	EN030493	14-Sep-51	female	42.0	226	14.5	1940	Staggered
22	AR090539	20-Sep-73	male	26.0	240	24.6	8454	28
23	PR110542	27-Oct-73	male	28.0	254	23.5	4372	Staggered
24	PW070642	18-Apr-53	male	44.0	252	24	1333	52
25	WL040348	21-Sep-60	male	34.0	312	10	6620	50
26	PS030595	07-Nov-49	female	45.0	1196	18	831	Unknown

Appendix 5.1: Patient invitation letter

Ref NO: 06/S1101/10
Version 2
Date: 16/03/06

Patient invitation letter

Title of the study: Effects of Acetylcysteine in the management of paracetamol overdose
Researcher: Dr. Nasrin Pakravan

Dear Sir/ Madam

You are being asked to take part in a study in which we are examining how you respond to the treatment you may receive. You have taken an overdose of paracetamol and may need treatment with an antidote which is routinely used for this condition. We are studying the effects of the antidote in a group of patient. Before you decide whether to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following carefully and ask if there is anything that is not clear, or if you would like more information. Please take time to decide whether or not you wish to take part and. If you do not wish to take part in this study it will not affect your treatment in any way.

Thank you for your time.
Yours faithfully,

Dr Nasrin Pakravan

Clinical Research Fellow

Appendix 5.2: Patient information sheet
(page 1)

Ref NO: 06/S1101/10
Version 2
Date: 16/03/06

Patient information sheet

Title of the study: Effects of Acetylcysteine in the management of paracetamol overdose
Researcher: Dr. Nasrin Pakravan

Dear patient:

You are being asked to take part in a study in which we are examining how your body responds to the treatment you may receive. You have taken an overdose of paracetamol and may need treatment with an antidote to protect you from the poisonous effects of the paracetamol.This antidote, NAC, N-acetylcysteine, protects your liver from very serious liver injury which occurs when paracetamol is taken in overdose. Unfortunately a small group of patients may suffer a range of side effects from treatment and we are trying to understand more about this so we can prevent it happening, or identify which patients are more likely to have a problem. These effects include in particular feeling sick, and flushed. As treatment is essential, if needed, this is an important practical problem for us, even though all these side effects can be treated successfully.

You are being asked to take part in this study as you have taken an overdose of paracetamol and you may need NAC as treatment. We are hoping to study 50 patients.

It is up to you to decide whether or not to take part. If you decided to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

If the drug level in your blood shows that you require NAC treatment and you agree to take part in this study, you will be asked to allow us to use the routine blood samples taken when you were admitted for this research, and to provide some extra blood samples (15 ml) just before, 15 min, 30 min, 1 hour and 2 hours after starting treatment with NAC. Taking extra blood samples involves insertion of an additional cannula (small plastic tube) into your arm.

Appendix 5.2 (page 2)

We are also asking your permission to use these clinical samples for research to measure some chemicals in your blood that may be involved in causing side effects.

To investigate better how your body responds to NAC, we need to accurately record your blood pressure, pulse rate, respiratory rate and temperature every half an hour till 2 hours and then every hour till 4 hours after start of NAC treatment and then as routinely to the end of your treatment.

To detect any change in your breathing, you will be asked to take a standard test involving a short sharp breath into a peak flow tube before and 1, 2, 4 hours after starting NAC and then every 4 hours to the end of your treatment which takes 20 hours.

Blood samples will be taken either by one of the nursing staff or myself. All the results will be kept anonymous, and your personal details will not be disclosed to a third party. If you agree we will inform your GP of your participation in the study.

This study has been reviewed by the Lothian Local Research Ethics Committee. If you have any further questions feel free to ask or contact the telephone number above.

Thank you for reading this information sheet.

Dr Nasrin Pakravan
Clinical Research Fellow

Appendix 5.3: Patient Consent Form

Ref NO: 06/S1101/10
Version 2
Date: 20/03/2006
Patient Identification Number ……

Patient Consent Form

Effects of Acetylcysteine in the management of paracetamol overdose
Researcher: Dr. Nasrin Pakravan

Please initial box

1- I confirm that I have read and understand the patient information sheet dated 16.03.2006 (Version 2) for the above study, and have had the opportunity to ask questions.
2- I understand that this study will normally involve me providing additional blood samples, to routine samples being taken during my time in the hospital. An additional cannula will be inserted in my arm for taking blood samples. My blood pressure, pulse rate, respiratory rate and temperature will be recorded more frequently than clinical routine. I also understand that a standard test of breathing involving me making a short breath into a peak flow tube will be measured for this study.
3- I understand that the results of the above samples will be used for research.

4- I understand that sections of any of my notes may be looked at by responsible individuals from the Scottish Poison Information Bureau and the Toxicology unit at the Royal Infirmary of Edinburgh or from regulator authorities where is relevant to my taking part in research. I give permission for these individuals to have access to my records.

5- I realise that my participation is voluntary and that I can withdraw my consent at any time without giving any reason, without my medical care or legal rights being affected.

6- I understand that my general practitioner (GP) will be informed from my participation in this study.

7- I agree that to take part in the above study. ☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of person taking consent (If different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Appendix 5.4: Data Collection Sheet

NAC Reaction Study
Study Ref No: 06/S1101/10
Version 1
Patient ID NO

Subject Data Collection Sheet

Date:

Patient study no:

CRN NO:

Patient's Initial

DOB:

Gender: Male Female Age:

Patient's weight (Kg) Patient's height (M)

Paracetamol overdose YES NO

Name of drugs taken

Alcohol consumption: before drug ingestion (h) with drug after (h)

Alleged amount of paracetamol (g):

Date of ingestion: Time of ingestion Staggered

Date of admission Time of admission

PMH such as liver disease, heart disease, Diabetes, allergic disease, HIV, ….

Drug Hx: Allergic Hx: Hay Fever Asthma Allergy to animal

Drug allergy Family history of allergy YES NO Unknown

History of NAC treatment YES NO Unknown

History of previous reaction to NAC YES NO Unknown

Alcohol consumption NO YES: Unit per week

High risk drug: NO YES

Phenobarbitone Phenytoin Carbamazepine Primidone

Rifampicin St John Wort Other

Paracetamol level hours after ingestion Location on R line:

Under high risk line Over high risk over normal treatment line

NAC treatment Reaction to NAC YES NO

Name of interviewer

Appendix 5.5: Observation Sheet

NAC Reaction Study
Study Ref No: 06/S1101/10
Version 1
Patient ID NO:

Observation Sheet

First bag of NAC
Date: Time started: Time finished

Second bag of NAC
Date: Time started: Time finished

Third bag of NAC
Date: Time started: Time finished

Time after start of NAC	BP	PR	RR	Tem	PEFR	Time recorded	Comment
0							
30 min							
1h							
2h							
3h							
4h							
8h							
12h							
16h							
20h							

NAC Reaction Study
Study Ref No: 06/S1101/10
Version 1

Adverse Reactions Sheet

Type of reaction	Time of initiation	Time of Termination	Treatment required	Other
Rash				
Pruritus				
Flushing				
Coughing				
Wheezing				
Dyspnoea				
Nausea				
Vomiting				
Chest Pain				
Abdominal Cramp				
Diarrhoea				
Fever (T ≥38)				
Hypotension (SBP<90 mmHg**)**				
Hypertension (BP>140 /90 mmHg				
Tachycardia (PR>120)				
Bronchospasm				
Abdominal Cramp				
Diarrhoea				
Angioedema				

Appendix 5.7: Blood Sampling Sheet

NAC Reaction Study
Study Ref No: 06/S1101/10
Version 1
Patient ID NO:

Blood Sampling Sheet

Sample / time point	0 (baseline)	15 min	30 min	1h	2h	4h	20h	Comment
tPA	3 ml			3 ml	3 ml	3 ml		
Histamine	3 ml	3 ml	3 ml	3 ml	3 ml			
NAC	3 ml		3 ml		3 ml	3 ml	3 ml	
Tryptase	3 ml		3 ml	3 ml	3 ml			
II,V,VII,VIII,IX,X	3 ml		3 ml	3 ml	3 ml	3 ml	3 ml	
vWf, IL6	3 ml		3 ml	3 ml	3 ml	3 ml	3 ml	
CRP/Paracetamol	3 ml			3 ml	3ml	3ml	3 ml	

Appendix 5.8: Plasma histamine (ng/ml) at baseline and time points after IV NAV infusion commencement and time of initiation and/or peak adverse reactions in the groups according to the severity of ADRs (intensive study), NS: no sample (intensive study).

Severity of ADRs	Subject No	Time between INAC infusion initiation and start/peak of adverse reactions	His 0	0min	His 1	15min	His 2	30min	His 3	60min	His 4	120min
Minimal	5	start at 40min	0.98	0	0.73	15	0.22	30	0.57	60	0.5	120
	6	start at 45min	0.44	0	NS	NS	NS	NS	0.69	60	0.32	120
	7	start at 80min	0.76	0	0.19	18	0.3	43	0.19	73	0.32	133
	9	start at 30min	0.26	0	0.24	17	0.24	33	0.41	68	0.25	128
	13	no reaction	0.82	0	0.53	20	0.73	40	0.72	70	0.84	120
	17	start at 20-40min	1.2	0	0.5	15	0.76	30	0.47	60	0.36	120
	18	start at 15 and 130min	1.41	0	0.71	15	0.7	30	0.7	70	1.83	190
	19	start at 55	0.17	0	0.75	15	0.38	30	0.97	60	0.4	125
	20	unclear time	0.52	0	0.39	20	0.68	35	0.55	70	0.82	120
	22	start at 15	0.35	0	0.31	15	0.35	35	0.37	65	0.28	140
Moderate	1	peak at 60 min	0.48	0	2.28	13	2.44	30	0.92	60	0.75	120
	2	start at 30-40	0.36	0	0.25	15	0.86	30	0.24	60	0.25	120
	12	start at 30-40	0.48	0	0.93	16	0.81	37	2.82	58	1.85	123
	15	start at 15-20	0.49	0	0.35	18	0.64	30	0.99	65	0.51	125
	21	start at 17 min	0.86	0	0.68	20	0.5	35	1.38	65	0.57	125
Severe	8	peak at 22 min	0.37	0	0.32	15	1.53	30	0.6	75	0.47	140
	10	peak at 35 min	0.27	0	0.27	20	1.33	35	0.27	60	0.26	120
	14	peak at 85min	0.5	0	0.29	15	1.76	35	1.13	70	0.81	135
	3	peak at 55min	0.62	0	0.24	15	0.11	30	2.16	70	0.78	120
	4	peak at 30min	0.79	0	0.58	15	0.68	30	1.34	60	0.39	120
	11	peak at 40min	0.42	0	0.53	15	1.09	35	1.82	70	0.9	130
	16	peak at 27min	0.49	0	0.93	17	0.53	35	1.48	65	0.33	125

Appendix 5.9: Plasma NAC concentration (µg/100µl) at baseline and time points (baseline, 1h, 2h and 4h) after IV NAC infusion commencement in each subject . NS: no sample. (1: minimal ADRs, 2: moderate ADRs, 3: severe ADRs) (intensive study).

Subject no	Severity	NAC baseline	NAC 30min	NAC 2h	NAC 4h	NAC 20h
1	**2**	0	9	4.75	4.25	NS
2	**2**	0.53	1.2	3.18	NS	2.3
3	**3**	0	12	4.5	2.75	1.7
4	**3**	0.3	NS	1	NS	NS
5	**1**	0.53	9.5	3.75	3.75	1.65
6	**1**	0	7.5	6.75	1	3.22
7	**1**	0	10.25	6.75	3.5	1.75
8	**3**	0	7.25	3.27	2.3	1.5
9	**1**	0	4.55	3.62	3.12	0
10	**3**	0	5.03	3.22	NS	NS
11	**3**	0	9.5	3.7	3.47	2.4
12	**2**	0	11.5	4.75	4.17	2.5
13	**1**	0	9.25	4.25	2.7	1.6
14	**3**	0	13	3.77	NS	NS
15	**2**	0	15	6.25	4.1	0.7
16	**3**	0.53	10.75	4.7	3.52	0
17	**1**	0	11.77	6.43	3.72	1.57
18	**1**	0	6	3	0.75	0.78
19	**1**	0	8.5	4.75	5.02	1.28
20	**1**	0	12.5	5.02	3.27	2.23
21	**2**	0	8.03	3.8	2	0
22	**1**	0.15	10.5	3.28	1	NS

Appendix 5.10: Plasma histamine concentration at baseline and different time points after IV NAC infusion in each subject in the group with minimal ADRs, N=10, His: Plasma histamine (ng/ml), T: time (min) ((Intensive study). NS: no sample (intensive study).

Subject No	His 0	T 0	His 1	T1 min	His 2	T2 min	His 3	T3 h	His 4	T4 h
5	0.98	0	0.73	15	0.22	30	0.57	60	0.5	120
6	0.44	0	NS		NS		0.69	60	0.32	120
7	0.76	0	0.19	18	0.3	43	0.19	73	0.32	133
9	0.26	0	0.24	17	0.24	33	0.41	68	0.25	128
13	0.82	0	0.53	20	0.73	40	0.72	70	0.84	120
17	1.2	0	0.5	15	0.76	30	0.47	60	0.36	120
18	1.41	0	0.71	15	0.7	30	0.7	70	1.83	190
19	0.17	0	0.75	15	0.38	30	0.97	60	0.4	125
20	0.52	0	0.39	20	0.68	35	0.55	70	0.82	120
22	0.35	0	0.31	15	0.35	35	0.37	65	0.28	140

Appendix 5.11: Plasma histamine concentration at baseline and different time points after IV NAC infusion in each subject in the group with moderate ADRs. N=5, His: plasma histamine (ng/ml), T: time (min) (intensive study).

Subject No	His 0	T 0	His 1	T15min	His 2	T30min	His 3	T1h	His 4	T2h
1	0.48	0	2.28	13	2.44	30	0.92	60	0.75	120
2	0.36	0	0.25	15	0.86	30	0.24	60	0.25	120
12	0.48	0	0.93	16	0.81	37	2.82	58	1.85	123
15	0.49	0	0.35	18	0.64	30	0.99	65	0.51	125
21	0.86	0	0.68	20	0.5	35	1.38	65	0.57	125

Appendix 5.12: plasma histamine concentration at baseline and different time points after IV NAC infusion in subjects with severe ADRs, N=7, His=plasma histamine (ng/ml), T=time (min), (intensive study).

Subject No	His 0	T 0	His 1	T1	His 2	T2	His 3	T3	His 4	T4
8	0.37	0	0.32	15	1.53	30	0.6	75	0.47	140
10	0.27	0	0.27	20	1.33	35	0.27	60	0.26	120
14	0.50	0	0.29	15	1.76	35	1.13	70	0.81	135
3	0.62	0	0.24	15	0.11	30	2.16	70	0.78	120
4	0.79	0	0.58	15	0.68	30	1.34	60	0.39	120
11	0.42	0	0.53	15	1.09	35	1.82	70	0.9	130
16	0.49	0	0.93	17	0.53	35	1.48	65	0.33	125

Appendix 5.13: histamine validation experiment: plasma histamine (ng/ml) in 8 healthy volunteers (4 male and 4 female). Samples were collected and cooled at once, but spun at different time points (5 min, 15 min, 30 min and 60 min) after collection. His: histamine; T: spinning time (minute after blood collection) (intensive study).

Subject no	T5min	His5min	T15min	His15m	T30min	His30min	T60m	T60min
1	5	0.48	15	0.491	30	0.333	60	0.374
2	5	0.503	15	0.992	30	0.693	75	1.293
3	5	0.829	15	0.644	30	0.764	60	0.483
4	5	0.562	15	0.686	30	0.831	60	0.803
5	5	1.006	15	0.548	30	0.374	60	0.618
6	5	0.488	15	0.744	30	0.583	60	0.479
7	5	0.483	15	0.386	30	0.344	60	0.419
8	5	0.785	15	0.587	30	0.782	60	0.817

Appendix 5.14: plasma tryptase concentration (µg/l) at baseline and time points (baseline, 1h, 2h and 4h) after IV NAC infusion commencement in each subject. NS: no sample. (1: minimal ADRs, 2: moderate ADRs, 3: severe ADRs) (intensive study).

Subject no	Severity	Tryp 0 µg/l	T0 min	Tryp 30m	T30min	Tryp1h	T 1h	Tryp 2h	T 2h
1	2	6.49	0	6.51	30	8.4	60	11.5	120
2	2	1	0	1	40	1	60	1	120
3	3	9.62	0	7.15	30	8.23	55	9.33	120
4	3	4.74	0	3.51	30	3.57	60	4.18	120
5	1	4.68	0	3.36	30	2.81	60	3.58	120
6	1	5.15	0	NS		1.53	85	3.76	145
7	1	2.65	0	1.62	40	1.99	72	2.06	132
8	3	1	0	1	40	1	75	1.67	135
9	1	1	0	1	33	1	68	1	128
10	3	3.69	0	NS	35	4.11	60	6.29	120
11	3	4.15	0	7.41	45	6.92	75	5.89	135
12	2	12.9	0	10.6	35	7.11	65	12.5	123
13	1	4.16	0	1.99	40	4.57	70	2.91	130
14	3	1.67	0	1	35	1	70	1.36	135
15	2	1.92	0	1.56	35	3.28	65	4.23	125
16	3	2.47	0	1.37	35	1.2	65	3.28	125
17	1	3.59	0	2.21	30	1.14	60	1.62	120
18	1	1	0	1	30	1	70	1	130
19	1	6.28	0	5.58	30	5.65	60	5.31	125
20	1	5.41	0	4.13	30		60	5.14	120
21	2	NS	0	NS	30	NS	60	NS	120
22	1	NS	0	NS	30	NS	60	NS	120

Appendix 5.15: plasma CRP concentration (mg/l) at baseline and time points (baseline, 1h, 2h and 4h) after IV NAC infusion commencement in each subject. NS: no sample. (1: minimal ADRs, 2: moderate ADRs, 3: severe ADRs) (Intensive study).

Subject no	Severity	CRP baseline	CRP 1h	CRP 2h	CRP 4h
1	2	10	10	10	
2	2	1	1	1	1
3	3	8	2	8	2
4	3	2	7	2	NS
5	1	1	1	1	1
6	1	1	1	1	1
7	1	1	1	1	1
8	3	1	1	1	1
9	1	1	1	1	2
10	3	50	NS	NS	NS
11	3	4	4	4	4
12	2	1	1	1	1
13	1	31	27	33	39
14	3	6	6	6	NS
15	2	4	4	4	4
16	3	1	1	1	1
17	1	1	2	2	2
18	1	NS	1	1	1
19	1	1	1	1	1
20	1	2	NS	2	1
21	2	1	1	1	7
22	1	8	8	7	7

Appendix 5.16: plasma IL6 (pg/ml) concentration at baseline and time points (baseline, 30 min, 1h, 2h, 4h and 20h) after IV NAC infusion commencement in each subject . NS: no sample. (1: minimal ADRs, 2: moderate ADRs, 3: severe ADRs) (Intensive study).

Subject no	Severity	IL6 baseline	IL6 30min	IL6 1h	IL6 2h	IL6 4h	IL6 20hh
1	2	5.9	2	0.7	3.6	1.3	NS
2	2	5.2	4.9	3.1	3.5	1.6	NS
3	3	4	3.2	4.8	14.3	13.5	NS
4	3	1.1	NS	1.4	3.3	NS	NS
5	1	1.1	NS	1.1	1.9	2.8	1.2
6	1	2.1	2	2.9	2	5.9	8.3
7	1	0.5	1.3	0.4	0.5	1.8	1.7
8	3	4	3.2	4.8	14.3	13.5	NS
9	1	3	2.2	2	2.2	2.5	1.9
10	3	2.8	NS	NS	5.5	NS	NS
11	3	0.4	0.7	1.2	2.8	1.8	NS
12	2	4.3	0.9	1.8	3.3	5	NS
13	1	31.2	29.6	33	31.4	34.6	28.4
14	3	2.4	2.2	1.8	2.3	NS	NS
15	2	16.3	22.6	9.9	21.1	21.9	NS
16	3	4.6	4	4.4	5.2	4.9	NS
17	1	19.4	10.9	18.8	14.3	9.5	NS
18	1	4	4.3	8.5	19.2	20.5	9.3
19	1	0.3	0.5	0.7	1.3	6.8	1
20	1	1.2	0.7	1.1	1.2	1.06	4.4
21	2	4.9	3.4	3	4	10.6	6.1
22	1	2.2	2.3	2	2.8	2.9	NS

Appendix 5.17: plasma tPA activity (u/ml) concentration at baseline and time points (baseline, 1h, 2h and 4h) after IV NAC infusion commencement in each subject . NS: no sample. (1: minimal ADRs, 2: moderate ADRs, 3: severe ADRs) (Intensive study).

Subject no	Severity	tPA act baseline	tPA act 1h	tPA act 2h	tPA act 4h
1	2	0.1	0.3	0.1	0.2
2	2	0.1	0.1	0.1	0.1
3	3	0.1	0.1	0.1	0.1
4	3	0.5	0.8	0.5	NS
5	1	0.2	0.1	0.1	0.3
6	1	0.1	0.1	0.3	0.3
7	1	0.4	0.6	0.4	0.3
8	3	0.7	2	0.8	0.2
9	1	0.1	0.1	0.1	0.1
10	3	NS	NS	NS	NS
11	3	0.6	1.7	0.9	0.9
12	2	0.6	0.2	0.5	3.1
13	1	0.1	0.1	0.1	0.1
14	3	0.8	1.7	0.9	NS
15	2	0.9	2.2	1.1	0.9
16	3	0.3	1.4	0.6	0.5
17	1	0.9	0.1	0.1	0.1
18	1	0.1	0.1	0.1	0.1
19	1	0.43	1.09	0.1	0.1
20	1	0.3	0.4	0.1	0.3
21	2	0.1	0.1	0.1	0.1
22	1	0.1	0.1	0.1	0.2

Appendix 5.18: plasma tPA antigen (ng/ml) concentration at baseline and time points (baseline, 1h, 2h and 4h) after IV NAC infusion commencement in each subject.NS: no sample. (1: minimal ADRs, 2: moderate ADRs, 3: severe ADRs) (Intensive study).

Subject no	Severity	tPA Ag baseline	tPA Ag 1h	tPA Ag 2h	tPA Ag 4h
1	2	14.5	13.1	12	10
2	2	3.2	8.8	14.8	14.2
3	3	99.6	88.9	94.9	97.5
4	3	8.4	6.8	6.8	NS
5	1	12.9	14.9	13.2	14.8
6	1	12.9	16.5	20.6	14.4
7	1	1.8	2.7	2.5	3.5
8	3	9.9	11.8	13.4	6
9	1	16.7	15.4	13.9	8.6
10	3	NS	NS	NS	NS
11	3	6	6.2	9.7	7.9
12	2	6.3	3.6	9.2	15.9
13	1	29.9	20.6	46.1	35.7
14	3	3.2	4.8	3.8	NS
15	2	8.7	14.8	12.8	6.8
16	3	6.1	11.5	6.1	6
17	1	16.6	16.6	35.3	31.2
18	1	17.5	15.6	19.2	23.8
19	1	8.6	10.9	14.9	33.8
20	1	54.1	48.9	19.9	53.9
21	2	29.8	40.6	29.4	18.9
22	1	17.7	13.5	19.3	6.1

Appendix 5.19: plasma vWf (ng/ml) concentration at baseline and time points (baseline, 30min,1h, 2h, 4h and 20h) after IV NAC infusion commencement in each subject. NS: no sample. (1: minimal ADRs, 2: moderate ADRs, 3: severe ADRs) (Intensive study).

Subject no	Severity	vWf base line	vWf 30min	vWf 1h	vWf 2h	vWf 4h	vWf 20h
1	2	1.09	2.83	0.68	0.97	0.94	NS
2	2	1.92	1.82	1.49	1.67	0.56	1.5
3	3	1	0.86	0.99	1.06	1.06	1.06
4	3	1.06	0.99	0.72	1.07	NS	NS
5	1	0.88	0.69	0.75	0.83	0.76	1.23
6	1	0.89	NS	1.84	1.91	1.03	2.3
7	1	0.97	0.52	1.04	0.88	1.13	1.14
8	3	1	0.86	0.99	1.06	1.06	1.66
9	1	1.7	1.69	1.93	1.98	1.56	NS
10	3	1.51	NS	NS	1.79	NS	NS
11	3	0.78	0.75	1.01	1.06	1.21	0.95
12	2	2.21	2.12	2.06	2.17	2.19	2.04
13	1	2.16	2.98	3.25	0.94	2.72	0.9
14	3	1.2	1.2	1.12	1.04		NS
15	2	1.57	2.58	NS	1.32	1.13	1.46
16	3	0.86	0.88	0.69	0.78	0.82	NS
17	1	1.57	1.85	2.44	2.01	1.85	1.59
18	1	0.8	0.72	1.74	1.17	1.37	1.58
19	1	1.79	1.4	1.51	1.3	1.53	1.27
20	1	1.92	2.07	1.62	1.83	2.08	NS
21	2	3.23	3.13	3.02	2.19	2.38	2.02
22	1	0.89	1.08	1.13	1.13	1.14	NS

Appendix 5.20: plasma clotting factor II concentration (iu/l) at baseline and time points (baseline, 30 min, 1h, 2h, 4h and 20h) after IV NAC infusion commencement in each subject. NS: no sample. (1: minimal ADRs, 2: moderate ADRs, 3: severe ADRs) (intensive study).

Subject no	Severity	FacII baseline	FacII 30min	FacII1h	FacII2h	FacII4h	FacII20h
1	2	0.95	0.717	0.878	1.01	0.936	NS
2	2	0.571	0.411	0.491	0.496	0.529	0.512
3	3	1.051	0.884	0.903	0.903	0.878	0.796
4	3	0.512	0.445	0.501	0.792	NS	NS
5	1	0.765	0.665	0.665	0.717	0.626	0.736
6	1	1.21	NS	1.051	1.01	0.89	1.35
7	1	0.807	0.853	0.83	0.571	0.726	0.972
8	3	0.745	0.649	0.558	0.726	0.717	0.786
9	1	0.736	0.665	0.507	0.476	0.491	0.476
10	3	0.991	NS	NS	0.878	NS	NS
11	3	1.238	1.139	1.187	1.212	1.265	1.094
12	2	0.847	0.755	NS	0.676	0.83	0.903
13	1	0.612	0.449	0.425	0.471	0.441	0.584
14	3	0.755	0.673	0.641	0.755	NS	NS
15	2	0.919	0.775	NS	0.818	0.83	0.89
16	3	0.736	0.517	0.491	0.584	NS	NS
17	1	0.851	0.691	0.701	0.719	0.691	0.803
18	1	0.717	0.591	0.641	0.605	0.649	0.393
19	1	1.03	0.853	0.736	0.919	0.936	0.954
20	1	0.936	0.807	NS	0.83	0.796	0.936
21	2	0.781	0.617	0.701	0.647	0.803	0.781
22	1	0.803	0.561	0.729	NS	0.749	NS

Appendix 5.21: plasma clotting factor V concentration (iu/l) at baseline and time points (baseline, 30 min, 1h, 2h, 4h and 20h) after IV NAC infusion commencement in each subject. NS: no sample. (1: minimal ADRs, 2: moderate ADRs, 3: severe ADRs) (intensive study).

Subject no	Severity	Fac V baseline	Fac V 30min	Fac V 1h	Fac V 2h	Fac V 4h	Fac V 20h
1	2	1.088	1	1.133	1.133	1.133	NS
2	2	0.238	0.238	0.256	0.256	0.244	0.262
3	3	0.716	0.716	0.74	0.829	0.719	0.694
4	3	0.768	0.651	0.74	0.697	NS	NS
5	1	0.526	0.526	0.657	0.694	0.575	0.827
6	1	0.827	NS	1.18	0.694	1.004	1.526
7	1	0.482	0.631	0.631	0.43	0.575	0.827
8	3	0.716	0.716	0.694	0.928	0.827	1.133
9	1	0.455	0.575	0.575	0.542	0.612	0.74
10	3	1.46	NS	NS	1.595	NS	NS
11	3	0.928	1.045	1.18	1.18	1.18	1.045
12	2	0.74	0.524	NS	0.797	0.928	0.994
13	1	0.651	0.651	0.542	0.716	0.694	1.088
14	3	0.455	0.51	0.355	0.542	NS	NS
15	2	0.542	0.716	NS	0.768	0.74	0.827
16	3	0.575	0.496	0.455	0.631	NS	NS
17	1	0.524	0.586	0.638	0.697	0.638	0.803
18	1	0.355	0.298	0.346	0.312	0.337	0.14
19	1	1.004	1.045	1.133	1.045	1.133	1.088
20	1	1.045	1.045	NS	1.18	1.18	1.231
21	2	0.771	1.039	0.994	1.039	1.086	1.039
22	1	0.404	0.471	0.524	NS	0.539	NS

Appendix 5.22: plasma clotting factor VII concentration (iu/l) at baseline and time points (baseline, 30 min, 1h, 2h, 4h and 20h) after IV NAC infusion commencement in each subject. NS: no sample. (1: minimal ADRs, 2: moderate ADRs, 3: severe ADRs) (intensive study).

Subject no	Severity	Fac VII base	Fac VII 30min	Fac VII 1h	Fac VII 2h	Fac VII 4h	Fac VII 20h
1	2	1.126	0.838	0.838	0.733	0.733	NS
2	2	0.419	0.272	0.286	0.259	0.217	0.217
3	3	0.392	0.268	0.263	0.239	0.231	0.226
4	3	0.79	0.621	0.65	0.6	NS	NS
5	1	0.698	0.508	0.444	0.534	0.409	0.52
6	1	1.126	NS	0.921	1.17	0.577	0.865
7	1	0.733	0.665	0.621	0.334	0.471	0.65
8	3	1.636	1.167	1.167	1.209	0.984	1.052
9	1	0.577	0.508	0.46	0.392	0.419	0.409
10	3	0.838	NS	NS	0.665	NS	NS
11	3	0.79	0.621	0.621	0.607	0.577	0.562
12	2	1.088	0.838	NS	0.812	0.77	0.784
13	1	0.635	0.439	0.392	0.392	0.313	0.562
14	3	0.483	0.37	0.336	0.336	NS	NS
15	2	0.838	0.65	NS	0.577	0.592	0.65
16	3	0.409	0.324	0.235	0.297	NS	NS
17	1	0.934	0.646	0.646	0.6	0.527	0.765
18	1	0.239	0.134	0.131	0.105	0.101	0.069
19	1	1.126	0.865	0.865	0.812	0.733	0.812
20	1	1.167	0.921	NS	0.865	0.79	0.838
21	2	0.754	0.489	0.501	0.466	0.434	0.527
22	1	0.569	0.363	0.363	NS	0.334	NS

Appendix 5.23: plasma clotting factor VIII concentration (iu/l) at baseline and time points (baseline, 30 min, 1h, 2h, 4h and 20h) after IV NAC infusion commencement in each subject. NS: no sample. (1: minimal ADRs, 2: moderate ADRs, 3: severe ADRs) (intensive study).

Subject no	Severity	Fac VIII baseline	Fac VIII30min	Fac VIII1 h	Fac VIII2h	Fac VIII4h	Fac VIII20h
1	2	0.791	0.752	0.64	0.657	0.733	NS
2	2	2.44	3.039	3.039	3.039	2.316	1.53
3	3	0.855	0.909	1.407	1.318	1.343	1.819
4	3	0.886	0.758	0.886	0.662	NS	NS
5	1	0.567	0.577	0.504	0.741	0.607	0.82
6	1	2.852	NS	3.011	3.964	2.403	2.193
7	1	1.094	1.665	1.004	0.725	0.897	1.391
8	3	0.95	1.158	0.728	1.057	1.223	1.294
9	1	1.294	1.33	1.395	1.282	1.381	1.235
10	3	1.158	NS	NS	1.934	NS	NS
11	3	0.577	0.768	0.851	0.931	0.89	1.241
12	2	1.437	1.222	NS	1.156	1.536	1.165
13	1	1.486	1.202	1.498	1.63	1.767	1.754
14	3	0.952	0.857	0.917	0.989	NS	NS
15	2	0.897	0.845	NS	0.938	0.945	1.202
16	3	1.559	0.521	0.464	0.68	NS	NS
17	1	1.282	0.938	1.212	1.212	0.982	1.146
18	1	1.641	1.414	1.658	1.461	1.702	1.425
19	1	1.193	1.346	1.848	1.379	1.617	1.313
20	1	1.949	2.405	NS	2.137	1.934	1.335
21	2	2.171	3.326	2.759	2.24	2.025	1.549
22	1	0.838	0.582	0.651	NS	0.73	NS

Appendix 5.24: plasma clotting factor IX concentration (iu/l) at baseline and time points (baseline, 30 min, 1h, 2h, 4h and 20h) after IV NAC infusion commencement in each subject. NS: no sample. (1: minimal ADRs, 2: moderate ADRs, 3: severe ADRs) iIntensive study).

Subject no	Severity	Fac IX baseline	Fac IX 30min	Fac IX 1h	Fac IX 2h	Fac IX 4h	Fac IX 20h
1	2	0.783	0.75	0.757	0.776	0.81	NS
2	2	0.812	0.453	0.447	0.426	0.426	0.389
3	3	1.113	0.914	0.99	0.922	0.922	0.906
4	3	1.044	0.845	0.964	0.763	NS	NS
5	1	0.486	0.367	0.537	0.636	0.565	0.738
6	1	1.548	NS	1.328	2.115	1.063	1.594
7	1	0.619	0.666	0.591	0.418	0.535	0.894
8	3	0.955	0.824	0.81	0.89	0.875	1.063
9	1	0.738	0.684	0.698	0.641	0.69	0.906
10	3	1.063	NS	NS	1.063	NS	NS
11	3	1.194	1.047	1.218	1.31	1.296	1.194
12	2	1.17	1.016	NS	0.903	1.006	1.036
13	1	0.682	0.575	0.56	0.619	0.494	0.745
14	3	1.112	0.877	0.718	0.939	NS	NS
15	2	0.948	0.796	NS	0.804	0.894	1.079
16	3	0.672	0.398	0.376	0.481	NS	NS
17	1	1.194	0.86	0.844	0.903	0.844	1.158
18	1	0.961	0.781	0.812	0.672	0.731	0.379
19	1	0.93	0.835	0.903	0.835	0.885	1.006
20	1	1.6	1.38	NS	1.409	1.31	1.583
21	2	1.27	1.047	1.101	1.016	1.146	1.101
22	1	0.912	0.679	0.718	NS	0.759	NS

Appendix 5.25: plasma clotting factor X (iu/l) concentration at baseline and different time (baseline, 30 min, 1h, 2h, 4h and 20h) points after IV NAC infusion in each subject with different severity. NS: no sample. (1: minimal ADRs, 2: moderate ADRs, 3: severe ADRs) (intensive study).

Subject no	Severity	Fac X base	Fac X 30min	Fac X 1h	Fac X 2h	Fac X 4h	Fac X 20h
1	2	0.617	0.537	0.584	0.566	0.56	NS
2	2	0.759	0.69	0.735	0.677	0.686	0.506
3	3	0.998	0.854	0.984	0.872	0.784	0.731
4	3	0.636	0.58	0.621	0.699	NS	NS
5	1	0.673	0.584	0.774	0.745	0.613	0.673
6	1	1.092	NS	0.938	1.632	0.656	0.805
7	1	0.577	0.717	0.58	0.417	0.515	0.64
8	3	1.07	0.793	0.763	0.858	0.793	0.911
9	1	0.671	0.604	0.555	0.555	0.614	0.625
10	3	1.07	NS	NS	0.635	NS	NS
11	3	1.21	0.974	0.997	1.021	1.021	0.841
12	2	1.045	0.875	NS	0.825	0.841	0.858
13	1	0.458	0.322	0.278	0.392	0.262	0.33
14	3	0.696	0.528	0.511	0.537	NS	NS
15	2	1.045	0.749	NS	0.709	0.735	0.793
16	3	0.693	0.426	0.414	0.528	NS	NS
17	1	0.952	0.709	0.696	0.709	0.683	0.778
18	1	0.841	0.636	0.647	0.583	0.564	0.271
19	1	1.021	0.809	0.841	0.841	0.809	0.778
20	1	1.273	0.974	NS	0.93	0.893	1.021
21	2	0.911	0.696	0.722	0.709	0.763	0.722
22	1	0.952	0.659	0.647	NS	0.671	NS

Appendix 5.26: plasma clotting factor XI concentration (iu/l) at baseline and time points (baseline, 30 min, 1h, 2h, 4h and 20h) after IV NAC infusion commencement in each subject. NS: no sample. (1: minimal ADRs, 2: moderate ADRs, 3: severe ADRs) (Intensive study).

Subject no	Severity	FacXI baseline	FacXI 30min	FacXI 1h	FacXI 2h	FacXI 4h	FacXI 20h
1	2	0.617	0.537	0.584	0.566	0.56	NS
2	2	0.759	0.69	0.735	0.677	0.686	0.506
3	3	0.998	0.854	0.984	0.872	0.784	0.731
4	3	0.686	0.58	0.621	0.699	NS	NS
5	1	0.673	0.584	0.774	0.745	0.613	0.673
6	1	1.092	NS	0.938	1.632	0.656	0.805
7	1	0.577	0.717	0.58	0.417	0.515	0.64
8	3	0.681	0.745	0.621	0.694	0.632	0.699
9	1	0.621	0.665	0.694	0.628	0.648	0.55
10	3	0.53	NS	NS	0.635	NS	NS
11	3	0.832	0.849	0.86	0.866	0.816	0.796
12	2	0.932	0.769	NS	0.849	0.838	0.895
13	1	0.243	0.24	0.238	0.272	0.243	0.235
14	3	0.726	0.669	0.673	0.694	NS	NS
15	2	0.849	0.779	NS	0.774	0.805	0.821
16	3	0.621	0.5	0.448	0.546	NS	NS
17	1	0.753	0.68	0.684	0.706	0.673	0.706
18	1	0.784	0.677	0.714	0.624	0.632	0.445
19	1	0.595	0.644	0.617	0.617	0.577	0.566
20	1	0.901	0.81	NS	0.816	0.779	0.779
21	2	0.953	1.04	0.998	0.974	0.9	0.725
22	1	0.537	0.462	0.453	NS	0.401	NS

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